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THE TREATMENT OF TUMOURS OF THE PAROTID GLAND
WITH SPECIAL REFERENCE TO TOTAL PAROTIDECTOMY

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So much attention has been directed to their fascinating variegated histology and to hypothesizing upon their origin, that practical problems relating to the permanent cure of mixed parotid tumours have been, to my mind, neglected. Obviously there is room for improvement in this direction.

The prognosis should be excellent. All will agree that every *potentially* malignant tumour should be curable. Even when a mixed parotid tumour has broken its confines, for many months it remains locally malignant only. Surely, one argues, the treatment of a tumour belonging to this category will not show depressing end-results; yet such is the case. Statistical inquiries reveal that the incidence of recurrence is considerable; in several series it is as high as 30 per cent, and this refers to tumours definitely encapsulated at the time of their removal. Although recurrence can take place after many years, R. Kennon showed that most of them occurred within twelve months.

When we examine the position regarding tumours which have recurred or are malignant already, I think there will be few who will disagree with what I have gleaned from first-class clinics up and down this country, viz., such cases are regarded with despondency. Fear of cutting the facial nerve and the bugbear of salivary fistula seem to deter surgical enterprise. Most of the patients are referred to the deep X-ray department, or are subjected to radium therapy.

It is my belief that by instituting some radical alterations in teaching and practice, all but a very few parotid tumours can be placed in a category where our conception of surgical pathology tells us they belong—absolute curability.

ESSENTIAL MODIFICATIONS OF CURRENT TEACHING

1. Most Tumours of the Parotid are Radioresistant.—Neoplasms consisting of highly differentiated cells (e.g., teratoma of the testis) do not respond to irradiation. Certainly in those cases of parotid tumour under my observation in which it was employed, deep X-ray therapy has proved futile, if not harmful. The following is a typical example:—

An Italian woman, aged 41, harboured a mixed parotid tumour for years. Six months previously it had commenced to show signs of malignancy. The surgeon she consulted

advised deep X-ray therapy. A full course of this treatment was given at a well-known centre, but the tumour continued to enlarge. I advised that total extirpation of the parotid gland should be attempted, and warned the family that the integrity of the facial nerve could not be guaranteed. A third surgeon was consulted, but advised against operation.

Distracted by the conflicting views, the patient went to Italy, where further advice was sought. I understand that more deep X-ray therapy was given without the slightest benefit.

To show how entirely radioresistant are most of these tumours, *Fig.* 214 is self-explanatory.

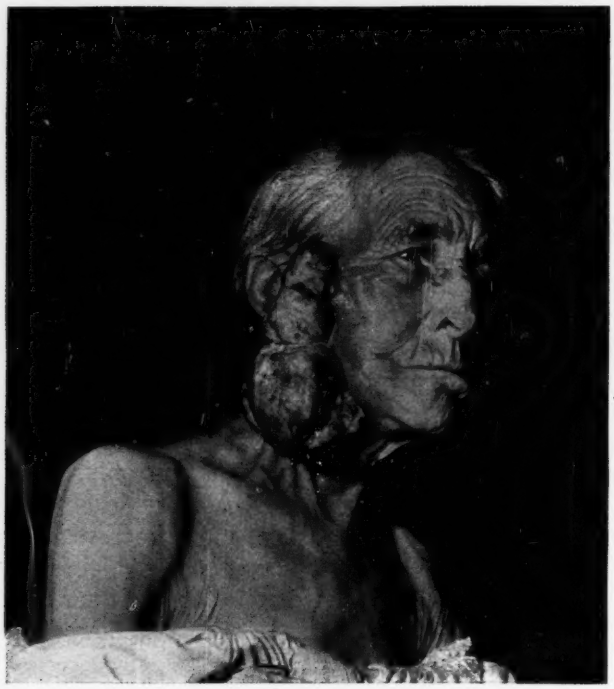

FIG. 214.—Three years previously this mixed parotid tumour became malignant. It has steadily progressed in spite of 51 exposures to deep X rays and 12 surface radium applications.

2. The Capsule of Encapsulated Tumours Must be Removed.—The usual technique is to incise the capsule and enucleate its contents. If recurrence is to be minimized, not only should precautions be taken to avoid spilling and implanting neoplastic cells, but the whole capsule must be removed completely by sharp dissection. These important considerations can be achieved in the following way :—

Both before opening the capsule and after enucleating its contents, the wound should be flooded with 60 per cent alcohol, or, as recommended by A. J. Ochsner, a 50 per cent solution of zinc chloride. Using a very sharp scalpel, the entire capsule is dissected from the parotid tissue (*Fig.* 215). If any structure is encountered which might be a branch of the seventh nerve, it is pinched lightly with dissecting forceps to see if facial twitching occurs.

3. Adequate Exposure Should be Employed.—McFarland has shown that it is the small, rather than moderate-sized or even large, parotid tumours which tend to recur. With inadequate exposure the smaller the tumour the more difficult

it is to be certain that it has been removed properly. So often, as soon as the capsule has been entered, a semi-solid mass of cells is extruded and the limitations of the capsule are lost irretrievably in the hæmorrhagic field. If the tumour and

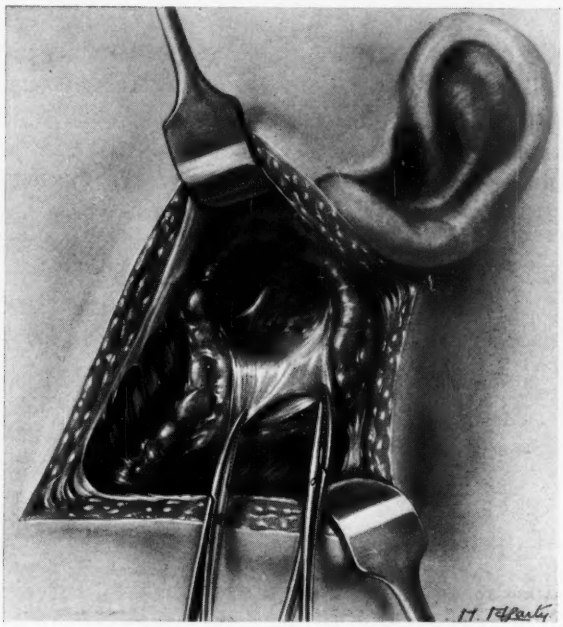

FIG. 215.—Removing the capsule of a mixed parotid tumour.

a reasonable amount of normal gland around it is displayed, ideal extracapsular dissection—that is total removal without entering the capsule—can often be effected.

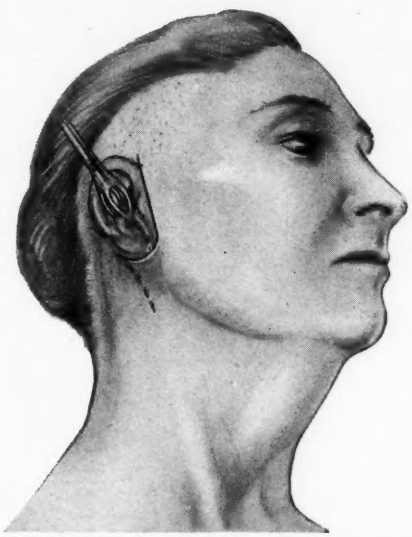

FIG. 216.—Blair's incision (modified) for exposing the whole parotid gland. The incision should be placed as near as possible to the cartilage of the ear. When it is desired to remove the whole parotid gland, the inferior end of the incision can be extended to the tip of the mastoid process and thence downwards along the anterior border of the sternomastoid.

Blair's incision (*Fig.* 216) gives extremely good access to the whole of the parotid gland. With the surrounding normal tissue, as well as the tumour, in view, complete extirpation without nerve injury is more likely to be effected than through a timid transverse incision. When the tumour is found to be non-encapsulated, the incision should be prolonged downwards and the external carotid artery ligated. The comparative avascularity following this step considerably aids efficient surgical treatment in difficult cases. Contrary to what might be thought, Blair's incision gives an excellent cosmetic result (*see Figs.* 221 and 224).

4. Salivary Fistula following Operations for Parotid Tumour is Extremely Unusual.—I have seen only one example of a salivary fistula following an operation for removal of a parotid tumour; the fistula closed spontaneously within three weeks. A perusal of the literature fails to reveal that a persistent parotid fistula has occurred sufficiently often to warrant it being listed as a deterrent to the radical surgical treatment of parotid tumours.

FIG. 217.—Diagrammatic conception of a coronal section through the parotid gland, showing the branches of the facial nerve sandwiched between the superficial and deep lobes.

5. The Surgical Anatomy of the Parotid Gland needs Revision.—The parotid gland consists essentially of a large superficial and a small deep lobe. These are joined by a comparatively small isthmus (*Fig.* 217), which is variable in size, but rarely absent (McWhorter).

The main trunks of the facial nerve, viz., the temporo-facial and cervico-facial divisions, embrace the

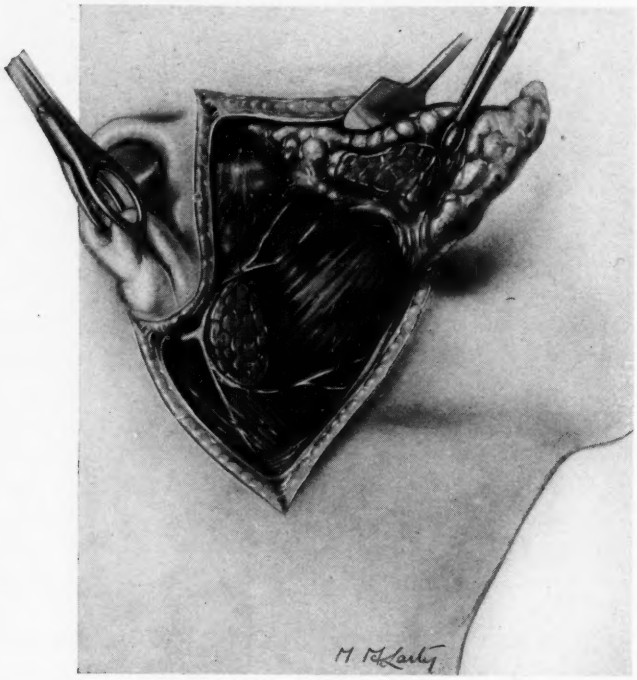

FIG. 218.—The superficial lobe of the parotid has been removed to show the temporo-facial and cervico-facial divisions of the facial nerve embracing the isthmus.

isthmus, but no part of the facial nerve runs actually within the gland substance. Rather, the facial nerve should be looked upon as the meat within a parotid sandwich, its main divisions lying between the deep and the superficial lobes; but because of the small size of the deep lobe, the outlying subdivisions of the nerve rest between the superficial lobe and the masseter muscle (*Fig.* 218).

The old conception of the parotid gland being constituted of a main mass with various projections passing deeply into surgically inaccessible and vulnerable recesses with the facial nerve traversing its parenchyma, should pass, as also should the teaching of that prince of surgical anatomists, Sir Frederick Treves, who taught that it was a surgical impossibility to remove the parotid gland in its entirety. On the contrary, complete extirpation of the gland with preservation of the facial nerve is a feasible undertaking for which there are definite indications.

6. Even when Facial Palsy Occurs, the Deformity can be Mitigated.—While one of the main objects of this paper is to show that the parotid gland can often be removed without sacrificing the facial nerve, the possibility of permanent facial palsy ensuing after extensive operations on the parotid must be expected in a proportion of cases—probably a higher percentage than has occurred in my small series.

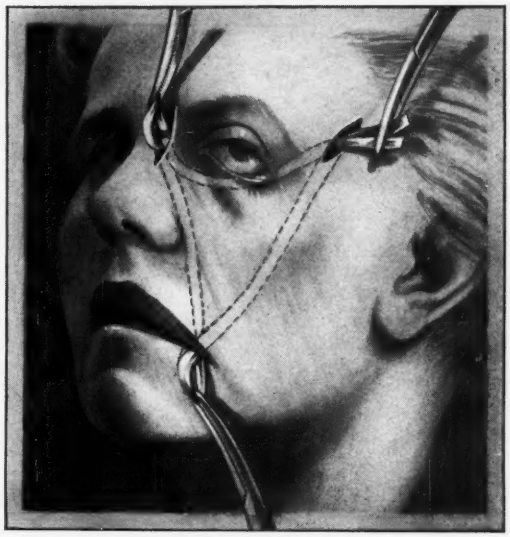

FIG. 219.—Lodge's method of inserting a strip of fascia lata to obviate the deformity of facial paralysis.

I am inclined to think that post-operative facial palsy is viewed by the profession too gravely, and often the hope of a permanent cure has been abandoned because of fear of severing the seventh nerve. It is probable that the prospect of permanent facial paralysis would be faced with more equanimity if the following facts were taken into consideration :—

a. By reason of increasing pressure of the tumour upon the nerve, facial palsy frequently occurs when surgical treatment is withheld; and

b. Lodge's method of inserting a fascial strip subcutaneously (*Fig.* 219), if performed comparatively early, considerably minimizes the baneful effects of this nerve lesion.

TECHNIQUE OF TOTAL PAROTIDECTOMY

When it has been decided to perform total parotidectomy, it is desirable to prolong the incision downwards along the anterior border of the sternomastoid, and as a first step to ligate the external carotid artery. I have carried out this measure in three instances and it makes the operation distinctly easier. The anterior skin-flap is reflected forward still farther in the neighbourhood of the mandible, a procedure which is rendered possible by the cervical extension. The submaxillary salivary gland within its capsule is located and, with this landmark, the posterior belly of the digastric is soon found. This is cleared so that it can

be recognized easily later in the course of the operation. We now set out to mobilize the superficial lobe of the parotid gland.

Mobilization of the Superficial Lobe.—The best place to commence is at the anterior extremity of its lower border (*Fig.* 220, A). Sistrunk advised isolating the inframandibular branch of the facial nerve as it runs along the angle of the jaw over the facial vessels as the first step in total parotidectomy, but I have found difficulty in finding the nerve before the gland has been freed. The anterior extremity of the lower border of the gland is a safe area as regards nerve injury and it constitutes an excellent place to get bearings. Having freed this corner of the gland, a new dissection is commenced diametrically opposite, i.e., at the extreme posterior end of the upper border of the gland (*Fig.* 220, B). The tragus

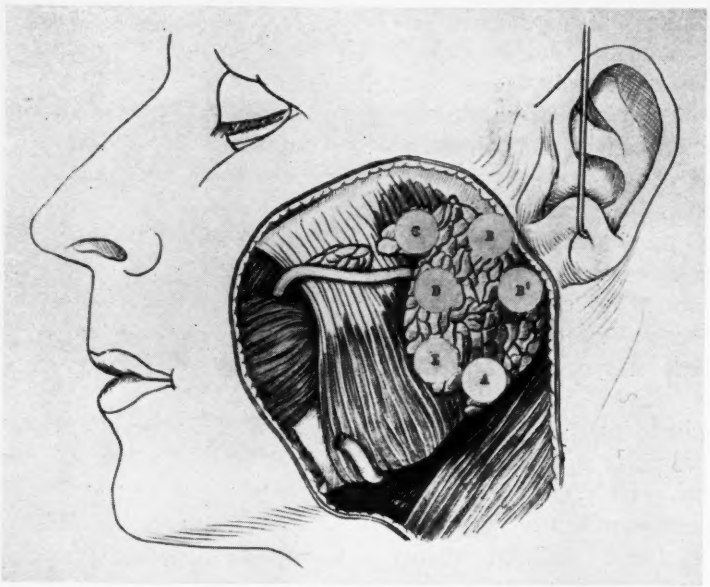

FIG. 220.—A plan for mobilizing the superficial lobe of the parotid gland. (*See text.*)

is grasped in Lane's tissue forceps and retracted well back, and a plane of cleavage will be found which allows the gland to be dissected up (*Fig.* 220, B¹). The temporal artery will be encountered here, but if the external carotid has been ligated, the empty vessel can be dissected up with the parotid, or left, whichever is more convenient. The dissection proceeds along the superior border and the gland is lifted from the zygomatic arch (*Fig.* 220, C). It is at this stage that great care is exercised and a sharp lookout kept for the uppermost parts of the pes anserinus. It is particularly important to preserve the upper branches going to the orbital region; like their fellows, they lie on the masseter muscle, and once a dissection is in the correct plane, there is no particular difficulty, for the nerves seem to adhere to the masseter rather than to the parotid. The dissection is continued along the anterior border (*Fig.* 220, D) and Stensen's duct and possibly the socia parotidis attached thereto are freed from the masseter, but there is no need to divide Stensen's duct at this stage. Again, in the middle region, the middle portions of the pes are seen, and the parotid is freed from them as far as convenient.

The lobule of the ear having been retracted strongly upwards and backwards, attention is directed to the only portion of the periphery of the superficial lobe which remains immobilized (*Fig.* 220, E). Grasping the antero-inferior border of the gland with Denis Browne's forceps, that portion which was mobilized as a first step (*Fig.* 220, A) is lifted up. The dissection proceeds towards the mastoid process, and, utilizing the upper border of the digastric muscle as a guide, the main trunk of the facial nerve can be identified.

Division of the Isthmus.—Having now the main trunk under vision behind and the gland mobilized at all sides, the limitations of the isthmus are sought by palpation. By retracting the superficial lobe forwards, the isthmus is divided with the scalpel from behind forwards. When this has been done, the facial nerve and its divisions will be clearly apparent. Stensen's duct is divided, if this has not been done already.

Removal of the Deep Lobe.—The facial nerve can be held aside by passing a ligature beneath it, and usually the deep lobe can be separated from the great vessels of the neck and the pharyngeal wall with comparative ease. Large tributaries of the jugular vein sometimes are a source of some embarrassment. In necessary cases there is no objection to ligating the jugular vein above and below its juxtaposition to the deep lobe, but this is rarely necessary.

There is no doubt that the anatomical arrangement of the isthmus is the seat of a certain amount of variation. Sometimes it is comparatively broad, but the main divisions of the facial nerve seem always to embrace it. I have not yet been able to satisfy myself as to the true arrangement of Stensen's duct in relation to the deep lobe. Apparently in all my cases the main ductules were connected only with the superficial lobe.

Why a parotid fistula has not followed in the two cases of superficial lobectomy I am not able to explain, for in both instances Stensen's duct was ligated.

CASE REPORTS

Case 1.—**Complete Excision of the Parotid Gland.**—Mrs. F. W., aged 46, for twenty years had a mixed parotid tumour. In March, 1935, the tumour was removed elsewhere; six months later it returned, and a second operation was performed. Recurrence soon followed, and she was treated by twenty-eight exposures of deep X rays, without benefit.

FIG. 221.—*Case* 1 (Mrs. F. W.), two years after complete removal of the parotid gland for recurrent mixed tumour.

I undertook complete removal of the parotid gland on March 4, 1938. Two years later, when this photograph was taken, there was no recurrence and no facial palsy (*Fig.* 221).

Case 2.—**Complete Excision of the Parotid Gland.**—Mrs. E. S., aged 50. For three years a lump had been noticed in the parotid gland. Six months previously it had increased in size, and had been growing fairly rapidly ever since.

On July 15, 1935, exploration showed a non-encapsulated tumour of the superficial lobe, and

total excision of the gland was undertaken. In spite of the fact that the facial nerve was dissected out in its entirety, paralysis, mainly of the temporo-facial division, was evident in the post-operative period. This persisted for several months, but showed gradual improvement (*Figs.* 222, 223).

When seen on April 17, 1940, the patient was perfectly well and all signs of palsy had disappeared.

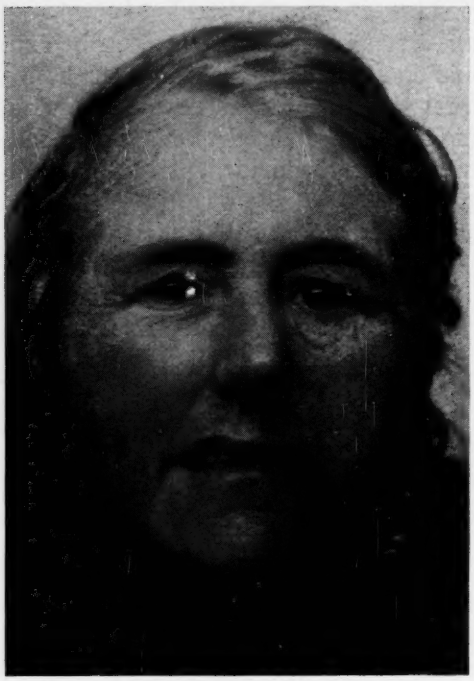

FIG. 222.—*Case* 2 (Mrs. E. S.), nine months after total removal of the parotid gland. The facial palsy is showing signs of improvement.

FIG. 223.—Same patient, showing the inconspicuous scar. At the end of two years the facial palsy had disappeared.

Case 3.—**Excision of the Superficial Lobe.**—Mrs. R. B., aged 30. Four years previously an operation for removal of a small mixed tumour of the parotid gland had been undertaken. For the past six months she had noticed a swelling which had increased in size.

On February 27, 1940, through Blair's incision, the superficial lobe of the parotid gland was excised. On examining the specimen it could be shown that the tumour was entirely confined to this lobe. In view of the fact that the patient was young and good-looking, I thought it inadvisable to remove the deep lobe and run the risk of facial palsy. I therefore cauterized the cut isthmus with the diathermy and closed the incision. The wound healed by first intention. There was no facial palsy or parotid fistula. The patient is at present serving in the W.A.A.F. Her husband informs me that she is perfectly well.

Case 4.—**Complete Excision of the Parotid Gland and Dissection of the Glands of the Neck, followed by Lodge's Operation.**—Mr. W. B., aged 61, for twenty-five years had had a small lump over the angle of the jaw. During the last two months it had grown rapidly. The tumour was commencing to involve the skin, and enlarged glands could be felt in the upper jugular chain.

On March 22, 1939, total removal of the parotid gland was undertaken, together with dissection of the glands of the neck. No attempt was made to isolate the facial nerve. The skin over the tumour was adherent to the gland, and the involved skin was excised with the parotid. Histologically the lymphatic glands were found to be involved in the neoplastic process.

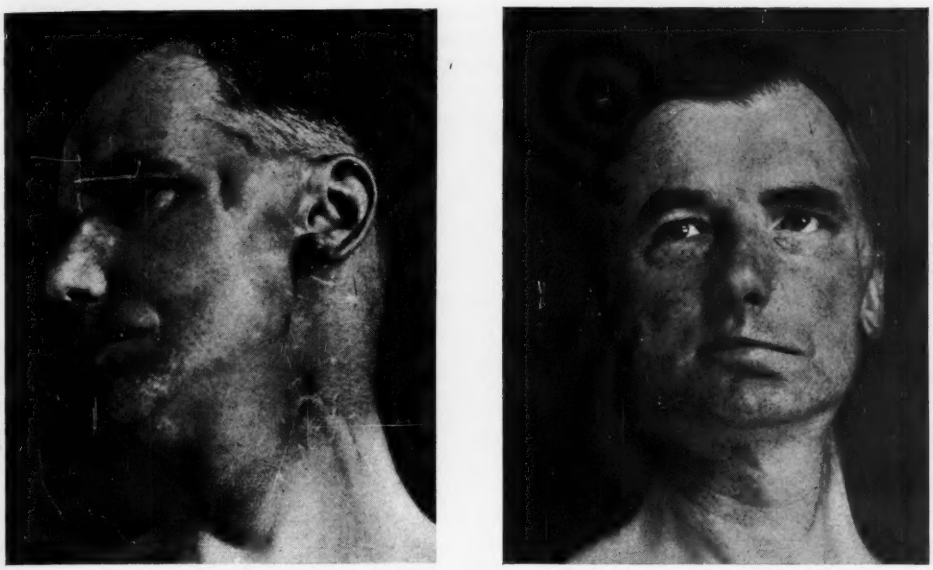

FIG. 224.—*Case* 4 (Mr. W. B.). Photographs taken eighteeen months after operation. No attempt was made to dissect the facial nerve. The whole parotid and some of the overlying skin and the jugular chain of lymphatic glands were removed, mainly with the diathermy knife. Three-and-a-half weeks later the ensuing facial palsy was to a great extent corrected by performing Lodge's operation.

On April 19, 1939, a strip of fascia lata was inserted by Lodge's method to help to correct the deformity of the facial palsy. Fifteen months later the patient was in good health and at work, and there was no sign of recurrence. At this time photographs were taken (*Fig.* 224). In November, 1940 his doctor reported that he was quite well.

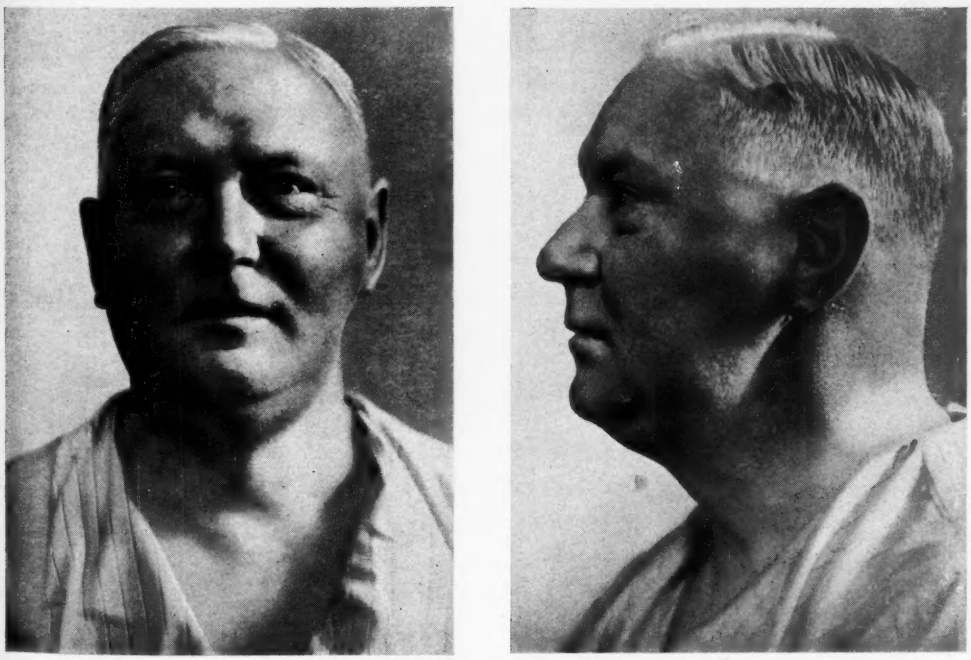

FIG. 225.—*Case* 5 (Mr. A. S.), one year after total removal of parotid gland with dissection of the glands of the neck.

Case 5.—**Complete Excision of the Parotid Gland and Dissection of the Glands of the Neck.**—Mr. A. S., aged 55. The patient was uncertain how long he had had the swelling, but at any rate for eighteen months it had been growing steadily.

Operation was undertaken on June 21, 1939. On exploring the tumour it was found to be non-encapsulated and total removal of the parotid gland was decided upon. When the incision had been prolonged downwards into the neck for the purpose of tying the external carotid artery, a chain of enlarged lymphatic glands was found in juxtaposition to the jugular vein; these were dissected out. Total removal of the parotid gland was performed and the facial nerve preserved. The histological report showed a mixed tumour of the parotid gland, but none of the lymphatic glands were involved—simple inflammatory hyperplasia alone was present. One year later the patient was in perfect health when the photographs were taken (*Fig.* 225). There is no sign of facial palsy.

It was the following case which first directed my attention to the bi-lobed surgical anatomy of the parotid gland, the possibility of preserving the facial nerve, and the astounding fact that a salivary fistula does not necessarily follow parotid lobectomy.

FIG. 226.—*Case* 6 (Mrs. E. R.), showing the extent of the parotid tumour.

Case 6.—As can be seen in *Fig.* 226, Mrs. E. R., aged 65, had a large parotid tumour. She stated that a lump had been present for many years, but it had only become conspicuous of late.

On February 25, 1937, I exposed the mass through Blair's incision. The tumour was found to be poorly encapsulated, and my endeavour was to remove the tumour with some normal tissue on all sides. Beginning from below, I dissected the gland from the angle of the jaw, then, proceeding from above, the gland was dissected from the masseter. Similarly, the dissection was recommenced from in front, and finally from behind. When I had thus mobilized the glandular mass containing the tumour, I was surprised to see that the branches of the facial nerve were not in the gland substance; it was possible to lift up what I now know to be the superficial lobe and remove it by severing the isthmus. Having seen the intact branches of the facial nerve clearly, I hoped that facial palsy would not follow, but I felt that a salivary fistula was a certainty. However, the wound healed by first intention and three and a half years later the patient is perfectly well.

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MESENTERIC VASCULAR OCCLUSION

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Occlusion of the mesenteric vessels is by no means a rare occurrence. It is surprising that the disease is so little known. A large recently published American *System of Surgery*, comprising no less than nine volumes, does not mention it, and the descriptions in most English surgical text-books are short and incomplete.

Although the underlying pathological lesions are many, the resulting clinical picture is fairly characteristic, and allows of a definite and accurate diagnosis in the majority of cases. The mortality resulting from the disease is still very high. As recently as 1938 Whittaker and Pemberton reported 19 cases with a mortality of 84 per cent following surgical intervention.

This review, together with a report of 8 cases all encountered within the last three years, is presented in the hope that further attention may be drawn to the condition. The present high mortality can only be reduced by earlier diagnosis and treatment.

HISTORY

To Tiedmann belongs the credit for the first case report in 1843. Virchow, four years later, followed with another case, and in 1854 added two more. It was not until 1895 that Elliot performed the first intestinal resection in treatment of the lesion. The disease began to attract attention after this, and numerous cases were reported and experimental studies made of the mechanism of the lesion. In 1904 Jackson, Porter, and Quinby reviewed the 214 recorded cases. The disease attracted little attention in this country until 1913. Trotter then presented his monograph based on 359 cases collected from the literature and 7 personal cases. Klein in 1921 made an exhaustive review of the disease. He could find only 24 cases of successful resections which had been reported. In 1923 Brady reported 14 cases. Three years later Cokkinis published a very comprehensive work based on 76 cases collected from the London hospitals, together with some original research on the mesenteric circulation.

More recently reviews of series of cases have been presented by Meyer (1931), Jones (1933), Dye (1935), Warren and Eberhard (1935), Whittaker and Pemberton (1938), and Fallis (1940), while single cases have been reported in this country by Raven (1937) and MacLeod (1937).

ANATOMY

In order to appreciate the underlying mechanism of the pathological changes in the disease, a knowledge of the anatomy of the blood-supply of the small and large bowel is essential. The blood-supply of the former is derived from the superior mesenteric artery, which also supplies the large bowel as far as the middle of the transverse colon. The large bowel distal to this is nourished by the inferior mesenteric artery.

The superior mesenteric artery arises from the aorta behind the pancreas, and passing forward in front of the third part of the duodenum enters the root of the mesentery. In this it passes downward and to the right, and ends near the cæcum by joining with the descending branch of the ileocolic artery. The superior mesenteric artery gives numerous branches. Ten to sixteen *intestinal branches* which are divisible into two groups, jejunal and ileal, pass from it between the layers of the mesentery towards the small intestine. Each divides into two branches which anastomose with those of adjacent arteries to form a series of arcades, from which secondary branches are given off. The process of division and union is repeated. In the case of the lower ileal arteries this may happen three or four times, so that four or five tiers of arches are formed. In the upper jejunum only one or two arches are present. From the terminal arcades straight vessels pass to supply the intestinal wall. These, called vasa recta, will obviously be longer the higher in the mesentery they are situated. According to Cokkinis there are no anastomoses between the vasa recta, but of course their areas of supply in the intestinal wall may overlap to some extent. The *inferior pancreatico-duodenal artery* arises from the proximal part of the superior mesenteric artery or its first jejunal branch. By joining with the superior pancreatico-duodenal artery, a branch of the gastroduodenal, it forms an obvious channel for the development of a collateral circulation in cases of occlusion of the superior mesenteric artery.

The middle colic artery arises from the upper part of the superior mesenteric artery, and passes forwards in the transverse mesocolon, where near the bowel it divides into left and right branches which anastomose with the right branch of the left colic and the ascending branch of the right colic arteries respectively. A marginal arcade is thus formed along the transverse colon.

The right colic and ileocolic arteries are also branches of the superior mesenteric artery. They pass to the right towards the ascending colon. Near the margin of the colon each divides into two branches. The descending branch of the ileocolic anastomoses with the termination of the superior mesenteric artery. The ascending branch joins the descending branch of the right colic, while the ascending branch of the latter joins with the right branch of the middle colic. The marginal arcade along the colon formed so far by the anastomoses of the branches of the middle, right, and ileocolic arteries, is completed on the left side in similar manner by the branches of the inferior mesenteric artery, which is itself a branch of the aorta. There is thus formed a marginal arterial arcade all round the colon. From it vasa recta pass to supply the large bowel. This is the common arrangement of the blood-supply of the colon, but a dissection of many bodies shows occasional examples of a pattern of arcades simulating those of the mesentery. With very minor alterations the venous drainage of the large and small bowel is patterned on that of the arterial supply.

THE RESULTS OF MESENTERIC OCCLUSION

When the blood-flow to any part is cut off the fate of that tissue depends on the rapidity of the development of a collateral circulation. The sudden fall of pressure in a main artery may be restored through the anastomoses of its branches with other vessels. If the occlusion is slowly brought about the collateral circulation is all the more likely to be sufficient to sustain the impoverished tissues. The superior mesenteric artery has a communication with the cœliac axis through the

anastomosis of the superior and inferior pancreatico-duodenal arteries. Distally there is an anastomosis with the inferior mesenteric artery through the inosculation of the middle and left colic vessels. These, however, are rarely sufficient to sustain the bowel where the superior mesenteric artery is suddenly blocked below the level of the inferior pancreatico-duodenal branch. When the obstruction is brought about slowly, however, no pathological change may occur in the bowel wall. From the anatomical arrangement of the arcades of the superior mesenteric artery it would appear at first sight that sudden blocking of any part of the artery or its branches should be easily circumvented. That such is not always the case is explained by secondary thrombosis which is caused by a temporary drop of blood-pressure in this arterial system and spreads to obliterate collateral channels. The vasa recta, on the other hand, are end-arteries with no communication with one another in the bowel wall. When two or three of these are obstructed so that the normal overlapping of their supply in the bowel wall is undone, pathological changes always follow. In the case of the veins, similar principles apply: the blocking of a number of vasa recta always leads to changes, while the results of obstruction in other parts of the venous arches depend on the possibilities of a collateral drainage. As in the case of the arteries, these may be occluded by secondary thrombosis. It has been shown experimentally that the first effect of reduction of the blood-flow to the bowel wall is tetanic contraction of its muscle. As the blood-flow in the intestinal vessels, which is normally slow, depends to some extent on intestinal muscle movements, this is a potent factor in leading to circulatory stagnation and spreading thrombosis.

The final result of the sudden and complete cutting off of the circulation through the mesenteric vessels is death of part of the bowel wall. As there are no valves in the veins, when the arterial pressure is suddenly lowered blood runs back into the part by *vis a tergo* and the affected area becomes infiltrated with blood. The bowel has thus the characteristics of other infarcted tissue. In very rare cases the cutting off of the entire arterial circulation to the bowel leads to anæmic death. Only 2 per cent of the cases collected by Trotter showed this change. Venous obstruction of course always leads to hæmorrhagic infarction.

Because the cases which come to surgical treatment are those in which infarction occurs, we are apt to forget that vascular disturbance may not always lead to permanent changes. It is not an uncommon occurrence to find other main arteries, in the limbs for example, completely obliterated, and yet no gangrene has resulted. When the blood-flow to the bowel is slowly cut off there may be no symptoms of mesenteric occlusion during life and no abnormality of the intestine at autopsy. Cases illustrating this have been reported, among others, by Schley, McCallum, Trotter, Chiene, and Howse. Again, because the symptoms and signs of acute mesenteric obstruction occur, although of course surgical treatment is the only rational method and the one with the greatest chance of success, where it has not been undertaken because of the poor condition of the patient, lack of diagnosis, or other causes, spontaneous recovery sometimes occurs. Such a case was reported by Karcher. This patient died (from another cause) seven weeks after the mesenteric occlusion had taken place, and the embolus in the superior mesenteric artery was demonstrated at the autopsy. There was no infarction of the bowel, but from the typical clinical history there was no doubt that temporary vascular intestinal changes had occurred. In some cases when the affected area found at

operation is small and it seems likely that spontaneous recovery will occur it may be sound practice not to perform excision. Reed reported two such cases in 1921, and two occurred in my series. Another possibility must be considered: after mesenteric occlusion the collateral circulation may be sufficient to sustain the life of the affected bowel if the general arterial blood-pressure is adequate. Many of these cases, however, are caused by emboli the result of heart disease. When the myocardium begins to fail, the collateral circulation with the general reduction in the blood-pressure may be no longer adequate, and late infarction of the bowel wall may occur. Cases illustrating this point have been reported by Pomner, Virchow, Cohn, Schnitzler, and Lepine. In cases in which the general circulation is weak it may take less than a complete blocking of the mesenteric vessels to lead to changes in the bowel wall. The most interesting possibility, however, is that after mesenteric occlusion the collateral circulation may be adequate to prevent pathological changes in the bowel wall, but not sufficient to allow of normal bowel function. Intestinal ileus thus results. Councilman in 1894, Garcia (1927), and Davis (1921) reported interesting cases illustrating this point. In 1913 Reich reported a similar case of intestinal obstruction. At operation there was dilatation of the small bowel for no apparent cause. No infarction was present. At autopsy some days later a partial obliteration of the superior mesenteric artery was found, but there was by this time definite infarction of the bowel wall. In this connexion *Case* 8 is very interesting. The patient suffered from intestinal obstruction due to a localized area of paralytic ileus caused by mesenteric embolism. The blood-supply was sufficient to keep the bowel alive, but was not sufficient to sustain normal function. Following a lateral anastomosis the patient made a complete recovery.

PATHOLOGICAL ANATOMY

Anæmic Infarction.—In this rare condition the bowel remains pale and atonic. Later the wall softens and putrefactive changes occur in it. Organisms spread easily to the peritoneum so that peritonitis ensues.

Hæmorrhagic Infarction.—The affected bowel is swollen and rigid. It is of a mottled red colour, which may be either quite bright red or a typical dark venous red. The bowel wall is infiltrated with blood. The mucosa is plum coloured and all the folds are very much swollen. The lumen is usually full of altered blood. Very soon small areas of gangrene of the mucosa occur and infection usually spreads through the devitalized wall. Where the obstruction occurs some distance from the bowel wall the mesentery shows similar changes. There is always an effusion into the peritoneal cavity and it is usually blood-stained. Microscopical examination shows that the bowel wall is completely infiltrated with blood.

AETIOLOGY

The circulatory obstruction may be either arterial or venous. The latter accounts for 75 per cent of the cases.

Arterial Obstruction.—This is due either to embolism or to thrombosis. The common sites for the emboli are the left auricle in mitral stenosis and the aortic or mitral valve in ulcerative endocarditis. Occasionally thrombosis on an atheromatous ulcer in the aorta gives rise to the embolus. Rarely pulmonary vein thrombosis, as in Virchow's case, or thrombosis in a patent ductus Botalli, as in

Klob's case, may be the site of the embolus. Embolism of the superior mesenteric artery is much commoner than of the inferior mesenteric. The fact that the direction of the former is much more in the line of the aorta than the latter is usually held to account for this, as emboli would tend to enter the superior mesenteric artery more easily.

Thrombosis of the superior mesenteric artery follows disease of, or pressure on, its wall. Arteriosclerosis or atheroma is the common lesion. This may be associated with diabetes: one such case occurred in this series. It is not unlikely that localized mesenteric thromboses account for many of the abdominal crises which occur in diabetic subjects. Occasionally an aneurysm of the superior mesenteric artery itself or of the abdominal aorta near it leads to thrombosis. Thrombo-angiitis obliterans may affect this vessel and lead to thrombosis. Occasionally abdominal tumours may press upon the artery and thrombosis follow.

Venous Obstruction.—This is always due to thrombosis. Although Woloschin formulated the concept of retrograde venous embolism and Reich described two cases where it may have caused mesenteric venous obstruction, there is no doubt that it plays little and probably no part in the aetiology of mesenteric venous occlusion. Thrombosis in many cases has no apparent cause. Thus a primary group has been described. There is no doubt, however, that the number of primary cases will diminish the more complete and detailed is the search for a cause. There are two main factors responsible for secondary mesenteric thrombosis: they are (1) Portal obstruction, and (2) Peripheral sepsis. Cokkinis believes that the latter is the most frequent underlying factor. The infection reaches the mesenteric veins from the bowel wall, and the commonest site is the appendix. Other predisposing lesions have been diverticulitis, ulcerative colitis, carcinoma of the rectum, or strangulated bowel. Although cases of mesenteric venous occlusion have been reported following such peripheral sepsis, in the great majority the clinical picture in such circumstances is that of portal pyæmia. The causes of portal obstruction are many and various. It may be thrombosis in the vein itself due to disease of its wall, or pressure on it from without, the possible causes of which are legion. Cirrhosis of the liver, however, is the commonest cause of the portal obstruction. Occasionally blood diseases, particularly polycythæmia rubra or leukæmia, may lead to mesenteric thrombosis.

CLINICAL FEATURES

The disease is characterized by the sudden onset of central abdominal pain. Shock may be a marked feature and the patient may feel quite faint. A constant abdominal pain persists, but is associated with severe attacks of colic. Vomiting is usually a marked feature from the beginning. Whatever is taken by mouth is immediately returned. In some cases there is absolute constipation for both flatus and fæces, but in others a bowel action occurs and consists of altered blood. In the late stages of the disease the picture is that of neglected intestinal obstruction. The abdomen becomes progressively distended. Vomiting is frequently repeated and is of intestinal type, and there is marked dehydration. On examination the patient's general appearance is very striking. He is pale and restless, the blood-pressure is low and the pulse poor and rapid. When massive infarction has occurred the picture is that of severe internal hæmorrhage, from which indeed the patient is really suffering. On abdominal examination distension is only

present in late cases. There is always tenderness and rigidity of the abdominal wall overlying the affected bowel. Sometimes the thickened coils of bowel can be palpated. In addition there is visible or audible evidence of increase of intestinal movements. Free fluid can usually be demonstrated. On rectal examination there may be a trace of blood on the finger.

DIAGNOSIS

According to the literature it is very uncommon for the condition to be correctly diagnosed. This occurred in only 4 per cent of Trotter's series. The clinical picture ought to be recognizable as that of mesenteric thrombosis. If on general examination there is a predisposing lesion—for instance, cardiac valvular disease—the condition is more easily diagnosed. A very important method of diagnosis is the administration of one or two enemata. This often leads to the evacuation of blood-stained fluid. Such a result is almost diagnostic. The most common misdiagnoses are acute hæmorrhagic pancreatitis, perforated peptic ulcer, and acute cholecystitis. When a careful history has been taken and adequate examination performed, it should be possible in the great majority of cases to make a correct diagnosis.

PROGNOSIS

The mortality of the disease, even after surgical treatment, is high. The lowest mortality-rate ever reported in a series of cases is in the region of 60 per cent. It can only be lowered by earlier correct diagnosis and treatment.

TREATMENT

It is imperative that abdominal exploration should be carried out at the earliest possible moment. It is important, however, to make the patient as safe for surgery as possible. Thus it is often necessary to administer saline and glucose by an intravenous drip for some hours before operation. If the blood-pressure is over 110 mm. Hg spinal anæsthesia is advisable. In very desperate cases it is possible to interfere using local anæsthesia only, supplemented if necessary by a little general anæsthesia.

When the abdomen is opened there is an immediate escape of blood-stained fluid and in many cases a curious and characteristic smell of putrefaction. The infarcted bowel is readily found, and should be excised with a good margin of healthy tissue. It is important to see that the affected mesentery is similarly treated, as thrombosis has a great tendency to spread from any portion of affected vessels left. The two bowel ends should then be closed and lateral anastomosis performed. In my experience exteriorization of the small intestine is a bad method of treatment and is always fatal. Even in the most desperate cases I believe it is always worth while carrying on with the anastomosis. If the patient dies on the table it is certain that no good would have followed exteriorization. In the rare cases where the large bowel is affected it is of course an excellent method.

AUTHOR'S SERIES

Eight cases have been encountered in the last three years: in 7 operation was undertaken; 1 had only a localized lesion and recovered without resection. One patient recovered following the short-circuiting of a segment of bowel which, due

to vascular disturbance, had lost its function; the remaining cases were all subjected to extensive intestinal extirpation, with a 60 per cent mortality. In one case a severe pre-operative chest infection made success almost impossible. Another patient lost his life because a piece of affected mesentery was left and a further spread of the thrombosis occurred. The recent work of Murray suggests that by the use of heparin this disaster might have been avoided. The last patient had many other associated pathological lesions, all of which helped to contribute to the fatal issue.

CASE RECORDS

Case 1.—**Mesenteric thrombosis due to cirrhosis of the liver; resection; recovery.**—Man, aged 59. Two days, lower abdominal colicky pain, vomiting, general distension of the abdomen, tenderness and rigidity in the right iliac fossa, increased peristalsis. Shifting dullness in the flanks. Blood in the rectum. Mesenteric thrombosis diagnosed.

Operation, spinal anæsthesia. Clear fluid. Five feet of ileum, red and thickened. Six feet of gut resected with thrombosed mesentery. Removed bowel was thick and rigid, the wall infiltrated with blood. Venous thrombosis of the vasa recta. Good recovery. Post-operative ascites.

Case 2.—**Mesenteric thrombosis, unknown cause; resection; further thrombosis; death.**—Man, aged 53. Septic finger, upper abdominal pain, vomiting, general abdominal distension, increased peristalsis, blood in the rectum. Emphysema and bronchitis. Mesenteric thrombosis diagnosed. Percaine spinal anæsthesia, much blood-stained free fluid. Four feet of ileum had typical mesenteric thrombosis; resection, anastomosis. Good recovery from operation, but died on the fourth day, with abdominal distension and vomiting. Autopsy showed that further thrombosis had taken place, with gangrene of the bowel and peritonitis. It would appear that not enough of the affected mesentery had been resected, so that further thrombosis occurred.

Case 3.—**Primary mesenteric venous thrombosis; resection; death.**—Woman, aged 69, lower abdominal pain, vomiting, marked abdominal distension, lower central region, rigidity and tenderness in right lower quadrant, visible peristalsis. Diagnosis of intestinal obstruction. Operation, general anæsthesia. Blood-stained free fluid. Two and a half feet of bowel thickened and congested, with thrombosed mesentery. Affected gut excised. Paul's tubes tied into the bowel ends. The resected bowel was dark purple, almost gangrenous; venous thrombosis. Died on the sixth day, having developed a left parotitis. Autopsy showed moderate atheroma of aorta and mesenteric vessels, also ulceration in the stomach and ileum.

Case 4.—**Diabetes; patches of mesenteric thrombosis; exploration and recovery.**—Woman, aged 70. Ten days of severe attacks of griping pains in the abdomen with vomiting. Abdominal distension in the central region, tenderness and rigidity in the right hypochondrium. Sugar in the urine. Operation under local anæsthesia. Some patches of mesenteric thrombosis, about four or five areas of the ileum about the size of a florin being affected; abdomen closed without resection. Recovery after treatment of the diabetic condition.

Case 5.—**Splenic anæmia; cirrhosis of the liver; thrombosis of the superior mesenteric vein.**—Woman, aged 36. Under treatment for more than six years for splenomegaly. Pain in the left of the abdomen and back. While in hospital undergoing investigation developed severe central abdominal pain, passage of blood by the rectum. Free fluid in abdomen. Death within 12 hours. Autopsy: complete thrombosis of the superior mesenteric vein; the whole of the small intestine showed hæmorrhagic infarction; the colon was full of blood; cirrhosis of the liver.

Case 6.—**Thrombosis of middle colic vein; resection of right colon; recovery.**—Woman, aged 54. Sudden severe griping pains across the lower abdomen. Repeated vomiting, blood by rectum, some tenderness in the right upper quadrant of the abdomen. Operation under spinal anæsthesia. Free blood-stained fluid; transverse colon was thick, doughy, and of mottled colour. Resection of the last few inches of ileum, cæcum, ascending

FIG. 227.—Coloured drawing of the resected bowel in *Case* 6. Inset shows a portion of the interior of the affected part of the bowel.

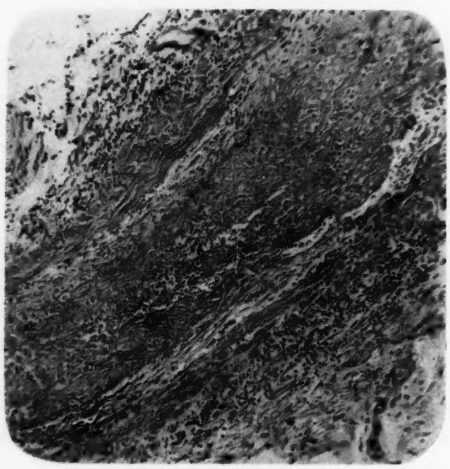

FIG. 228.—Longitudinal section of one of vasa recta veins, showing ante-mortem thrombosis. (× 64.)

and transverse colon, lateral anastomosis. The removed bowel showed old blood-clot in the lumen, wall thickened and infiltrated with blood (*Fig.* 227). The thrombosis was confined to the vasa recta veins and those in the bowel wall. Microscopical examination showed thrombosis of the vasa recta veins (*Fig.* 228). Uninterrupted recovery. It is unusual for primary venous thrombosis to affect the colic vessels.

Case 7.—**Primary mesenteric venous thrombosis; resection; death.**—Man, of 61. Fainting and vomiting about one hour after a meal. Severe abdominal pain, with recurrent spasms. Bloody stool. Lower abdominal distension, tenderness, and rigidity. Free fluid. Severe bronchitis. Mesenteric thrombosis diagnosed. Operation under local, supplemented by general, anæsthesia. Much free blood-stained fluid. About 4 ft. of ileum was affected with thrombosis, 2 ft. above the ileocæcal valve. The mesentery was affected for a depth of about 2 in. Resection; lateral anastomosis. The removed bowel showed the typical appearance of mesenteric thrombosis; the thrombosis was confined to the vasa recta veins and the vessels in the bowel wall. Death on the third day from bronchopneumonia. Autopsy showed anastomosis to be intact and no intra-abdominal abnormality.

Case 8.—**Auricular fibrillation; mesenteric embolus; lateral anastomosis; recovery.**—Woman, aged 68. Sudden severe pain in the lower abdomen. Vomiting, marked abdominal distension, visible peristalsis. Very irregular pulse, due to cardiac dilatation, and auricular fibrillation. Operation postponed for six days to give time for improvement of the pulse. Abdomen opened, right lower paramedium incision; much blood-stained free fluid. Five feet from ileocæcal valve a segment of gut was rigid and ecchymosed, one intestinal arcade was completely thrombosed. Lateral anastomosis performed above and below diseased area. Good recovery. Apparently a localized embolism had taken place in part of the superior mesenteric artery, leading to thrombosis of one of the intestinal arcades.

SUMMARY

1. The literature of mesenteric thrombosis is reviewed.

2. The aetiology, pathology, diagnosis, and treatment are considered.

3. It is suggested that a pre-operative diagnosis should be possible in the great majority of cases.

4. Eight personal cases are presented.

My thanks are due to Mr. H. H. Rayner, under whose care most of these cases were admitted to hospital, for granting me permission to quote them in this paper; also for his great kindness in giving me the opportunity to be associated with *Case* 6, which occurred in his private practice, and allowing me to include it in this series. *Case* 8 was admitted to hospital under the care of Mr. W. R. Douglas, and I am greatly indebted to him for allowing me to include it in this paper.

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SEMINOMA IN AN ABDOMINAL TESTIS WITH A GLIOMA OF THE BRAIN

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THE occurrence of malignant disease in an undescended testis is of interest on account of its rarity and on account of the difficulties which the diagnosis may present.

The occurrence of malignancy in normally placed and undescended testes has been reviewed by a number of workers, and whilst both malignant testis and undescended testis are relatively uncommon, the combination of the two conditions is sufficiently frequent to justify the belief that non-descent renders the testis more liable to malignancy. Rea (1931) states that the frequency of undescended testis has been variously recorded as 0·1 per cent (Marshall), 0·12 per cent (Monod and Terrilon), 0·22 per cent (Austrian Army), and 0·31 per cent (War Dept. World War). If from these figures one accepts that approximately 0·2 per cent of the male population suffers from undescended testis, then if non-descent did not affect the frequency of malignant disease, about 0·2 per cent of the observed cases of malignant testis should occur in patients with maldescended testis. In point of fact Rea records that out of 1371 malignant testes coming under the observation of six authors, 9·9 per cent* were undescended. That is, malignant disease of the undescended testis is approximately fifty times as frequent as it should be if maldescent carried no increased risk of malignancy; or, in other words, maldescent enhances the liability to malignant disease fifty times. Other workers give figures which differ from these, but which point to the same general conclusion.

Table I.—INCIDENCE OF ABDOMINAL AND INGUINAL MALIGNANT TESTIS

Author	*Testes Malignant*	*Malignant Undescended Testes*	*Inguinal*	*Abdominal*
Eccles	38	2	1	1
Howard	57	9	9	0
Bulkley	13	2	0	2
Chevassu	113	15	10	5
Meiser	—	68	64	4
Rea	76	11	5	6
Gordon-Taylor and Till	50	15	7	8
Coley	64	12	5	7
			101	33
			3	1

* Hinman (1924) found the proportion of undescended malignant testicle as high as 12·2 per cent in a series of 649 tumours.

As regards the relative frequency of abdominal and inguinal malignant testis, the combined figures given in *Table I* show 33 abdominal to 101 inguinal—that is approximately 1 : 3. There are apparently no reliable figures from which one can ascertain whether abdominal testis is more or less liable to malignancy than inguinal testis.

In view of the frequency of malignant disease in the undescended testis, it would be of the greatest interest to know whether orchidopexy tends to prevent such susceptibility. Gordon-Taylor and Till (1938) record 2 cases of malignant testis following orchidopexy and 1 following abdominal replacement. Similar cases have been recorded by Lund (1924), Cunningham (1921), Coley (1915), and Chevassu and Carrillon (1938). Such reports are too few to be significant, though their very scarcity does suggest that orchidopexy may lessen the tendency to malignancy, especially as such cases are particularly likely to be reported in the literature.

Symptoms are absent at an early stage in the disease unless torsion occurs. Vague symptoms such as slight abdominal discomfort, anorexia, constipation, and bladder pressure may be present. The tumour is at first lateral, in the iliac fossa, and not mobile: very occasionally the mass can only be felt per rectum. Symptoms and signs due to œdema of the legs, varicocele, or hydronephrosis are associated with the disease when advanced. Right-sided disease is more common than left.

The diagnosis of malignant undescended testis can be extremely difficult. The most frequent error is a failure to note that the testis is not in the scrotum, for once the possibility of testicular tumour is considered, the diagnosis can usually be made. This is especially true since the introduction of the Zondek-Aschheim reaction. According to Evans et al. (1933) this test is positive in the majority of malignant testicular tumours if it is performed quantitatively, and, further, the intensity of the reaction indicates the type of tumour present.

The reports in the literature of the pathology of testicular tumours are unreliable, since most of the earlier cases were reported as sarcomata. It has since been shown that the majority of these are really teratomata. Ewing (1934) holds that all malignant testicular tumours are basically teratomata, but often with one cell type predominating. Dew (1925) takes a similar view, but excludes the seminomata, which he regards as a separate type of tumour. In the present paper we have accepted Dew's nomenclature.

Owing to the difficulty of early diagnosis very few cases have been known to survive operation for a number of years. In Bulkley's (1913) series of 47 cases operated upon, only 3 were known to be alive and well after two years. Modern X-ray therapy does not appear to have altered this gloomy prognosis, so it is worth considering whether removal of an abdominal testicle is justified as a preventive measure if orchidopexy is impossible or has failed. It is worth mentioning, however, that Cabot, of the Mayo Clinic, has recently successfully brought down abdominal testicles in 4 cases (3 of them were bilateral). Although he recognizes that undescended testicles are much more liable to become malignant than fully descended ones, Cabot assumes that a successful orchipodexy minimizes the danger. It is unjustifiable to remove bilateral abdominal testicles before secondary sexual characters have developed, because there is no recorded case of malignant abdominal testicle before the age of 17. The removal of a unilateral undescended testicle which

cannot be placed in the scrotum appears justified, especially after puberty, because the organ is unduly liable to malignancy and yet there is no risk of its loss giving rise to hormonal deficiency.

CASE REPORT

Male, aged 55. Married, no children. Admitted to Bootle General Hospital June 3, 1939, as a case of cerebral thrombosis. He had been passed for the army in 1916 and had sustained a fracture of the humerus which had remained ununited. He was in normal health until a week before admission, when he developed headaches centred over the vertex. At 9 a.m. on the day before admission he suddenly collapsed and was found lying on the ground. Immediately afterwards he had about twenty epileptiform fits. He was admitted next day.

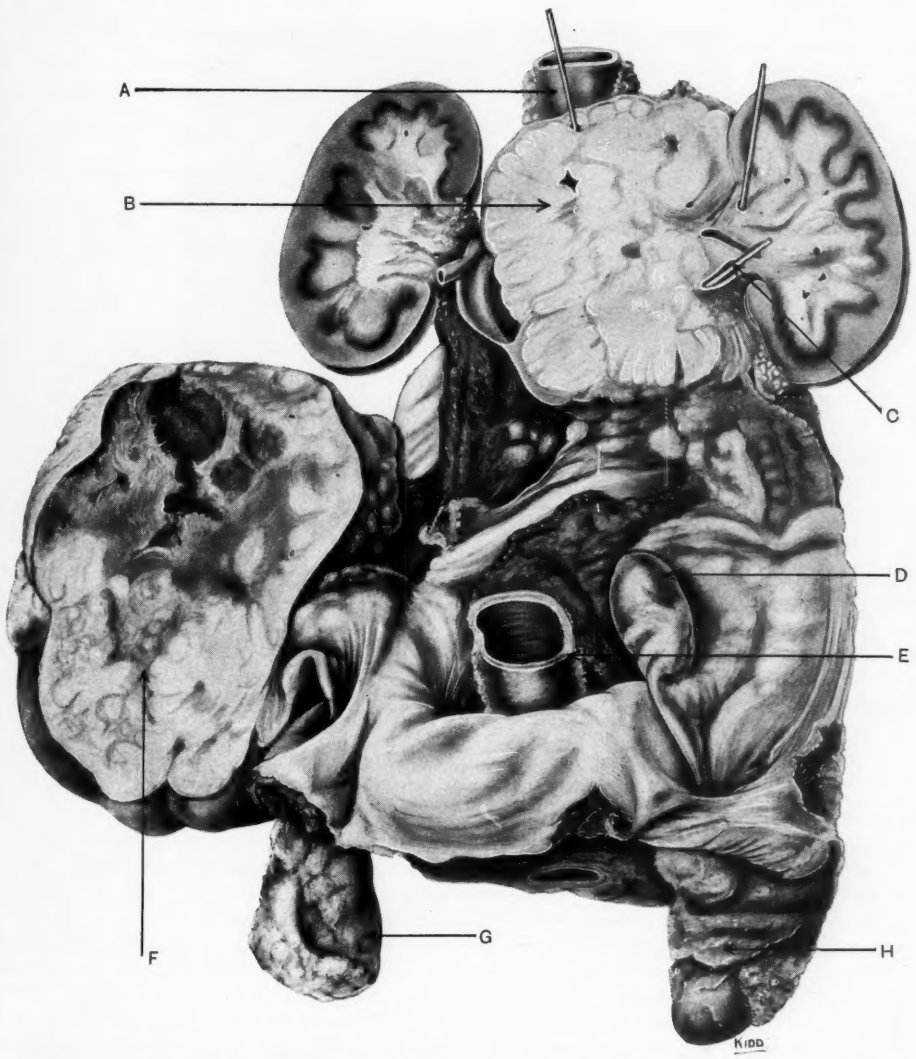

FIG. 229.—Showing the malignant right abdominal testicle with pre-aortic metastases. The left abdominal testicle and the bilateral inguinal hernial sacs are also shown. A, Abdominal aorta; B, Metastasis surrounding superior mesenteric vessels; C, Compressed left renal veins; D, Left abdominal testicle; E, Pelvirectal junction; F, Seminoma of right abdominal testicle; G, Right inguinal hernial sac; H, Left inguinal hernial sac.

CLINICAL FINDINGS.—Pupils contracted, light and conjunctival reflexes absent. Arms flaccid, with absent reflexes. Blood N.P.N. 57 mg. per cent. Lumbar puncture, pressure 350 mm. Total protein 240 mg. per cent. Chlorides 780 mg. per cent. Colloidal gold 4 4 4 3 3 3 2 1 0 0. First seen by one of us (M. J. B.-J.) eleven days after admission. Large fixed smooth mass in right iliac fossa. No testes present in scrotum or inguinal canals. Penis and secondary sex characters normal. Slight inco-ordination of left arm and leg, with loss of tactile discrimination. Extensor plantar response on left side. Bilateral papillœdema. Radiography of skull suggested increased intracranial tension. Zondek-Aschheim reaction negative, but prolan A present. Died July 1, 1939, twenty-eight days after admission. Clinical diagnosis : malignant abdominal testis with secondary deposit in the right cerebral hemisphere.

POST-MORTEM EXAMINATION.—Autopsy was performed six hours after death. The body was that of a rather poorly nourished male of middle age with an ununited fracture of the

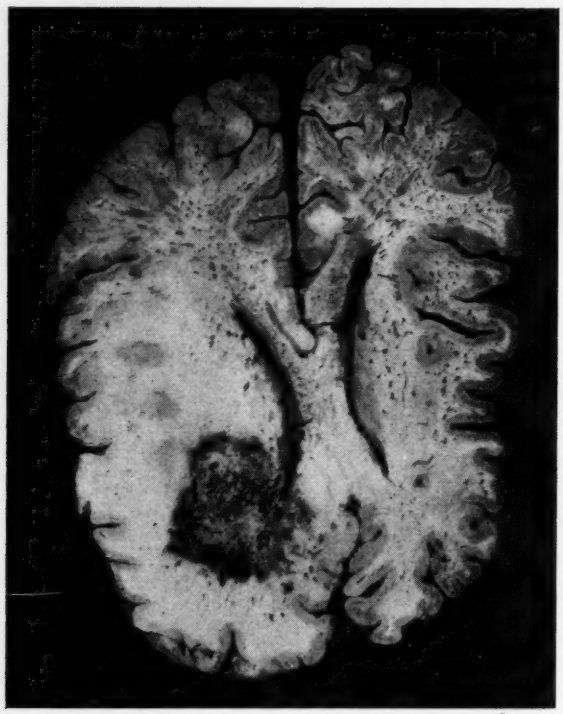

FIG. 230.—Showing the primary tumour in the brain which led to the diagnosis and the death of the patient.

shaft of the left humerus. The scrotum was empty. There were small inguinal herniæ on both sides. On the left side the testis lay just above the internal inguinal ring. On the right side the testis was replaced by an ovoid white tumour, 18 × 13 × 10 cm. (*Fig.* 229). The outer surface of the tumour was slightly nodular. On section, the cut surface was creamy-white and homogeneous, except in the upper half, where it had undergone degeneration and necrotic changes, forming ragged-walled cysts containing watery fluid. No remnants of normal testis could be found, though the spermatic cord could be traced into the tumour. A few enlarged, malignant lymph-glands could be traced running along the brim of the pelvis and upwards along the aorta to join a larger mass of glands at the level of the kidneys. This mass measured about 12 × 8 × 6 cm. and lay across the front and along both sides of the aorta, surrounding the proximal portions of the cœliac axis and superior mesenteric arteries, and the whole of the left renal artery and vein. It also surrounded the proximal part of the left ureter. The right renal vessels and ureter were unaffected. The cœliac

axis and superior mesenteric arteries and the left ureter were not narrowed, but the left renal artery and vein both appeared compressed, though no ischæmic changes could be found in the kidney.

No deposits of tumour were found in any of the viscera apart from the brain; and no lymphatic deposits were found above the level of the diaphragm. The bones of the limbs were not examined.

Brain: On opening the skull, the brain was found to be under tension and showed asymmetry, the right hemisphere being larger than the left. There was a rounded tumour (*Fig.* 230), 4 cm. in diameter, in the white matter of the right frontal lobe, adjoining and anterolateral to the tip of the anterior horn of the lateral ventricle. It was fairly well demarcated from the brain, greyish-white in colour, and traversed by numerous small vessels. It also showed some minute hæmorrhages. The remainder of the brain showed no signs of tumour.

HISTOLOGY.—Numerous sections were taken from different parts of the primary tumour. All showed similar histology—namely, that of a typical anaplastic seminoma. The tumour consisted of sheets of cells separated by strands of fibrous stroma carrying blood-vessels. The tumour cells were uniform, about 12–13 μ, with a rather scanty cytoplasm and a central round nucleus. The latter showed a sharp nuclear membrane, coarsely stippled chromatin pattern, and a prominent eosinophil nucleus. A considerable portion of the tumour was necrotic. One section of a nodule at the base of the tumour to which the cord led was found to contain a few epididymal tubules. Sections of the metastases in the abdominal lymph-glands showed an exactly similar appearance.

The tumour in the brain proved to be a glioma and not a metastasis as previously suspected. The histological structure was clearly that of an astrocytoma of well-differentiated type.

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DUODENAL DIVERTICULA AND THEIR COMPLICATIONS WITH PARTICULAR REFERENCE TO ACUTE PANCREATIC NECROSIS

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In his recent book on *Diverticula and Diverticulitis of the Intestine*, Edwards (1939) states that " the association of pancreatitis with diverticula of the second part of the duodenum has received considerable attention in the literature. . . . The association is a vague one. . . . It may be—and indeed is usually likely to be—accidental. . . . A further possibility is the causation of pancreatic disorder by the pressure of a ' perivaterien ' diverticulum upon the pancreatic duct at the ampulla of Vater. There has, however, been no authentic description from post-mortem findings of such an occurrence." In the light of these comments, the 4 cases reported below are noteworthy in two ways: first, they show that a perivaterine diverticulum may produce definite obstruction of the pancreatic duct; secondly, they indicate that the association of acute pancreatic necrosis with a perivaterine diverticulum is probably neither vague nor accidental, but that these conditions may reasonably be related as effect and cause through this very factor of duct obstruction. Finally, in the discussion of this series of cases, the opportunity is taken to review the complications of duodenal diverticula as revealed by a study of the literature.

CASE REPORTS

Case 1.—

Clinical History.—For nine weeks a miner, aged 69, had complained of a yellow face, dark yellowish-brown urine, poor appetite, excessive thirst, loss of weight, and clay-coloured stools. His previous history revealed nothing of importance.

The patient was ill nourished and definitely jaundiced. His abdomen was scantily covered, but moved freely on respiration. There was no increase of muscular resistance and no palpable mass, although slight discomfort was elicited on deep palpation in the epigastrium to the right of the middle line. The gall-bladder could not be felt. No free fluid was present and there was no enlargement of the liver or spleen. Digital examination of the rectum revealed nothing abnormal and the stool gave a negative benzidine reaction. A fractional test-meal yielded average figures. The pulse was increased to 112 per minute and there was some frothy bile-stained sputum, but otherwise the cardiovascular and respiratory systems were normal. The urine contained much bile and the icteric index was 83, while the van den Bergh reaction was biphasic.

After being admitted to hospital, the patient showed increasing jaundice, complete loss of appetite, and a temperature which swung between 98° F. and 102° F. Ultimately, he became comatose, and died seventeen days after admission. The provisional diagnosis was carcinoma of the head of the pancreas.

Post-mortem Examination.—

Macroscopical.—The body was that of a well-built, elderly, moderately jaundiced male. The duodenum showed two round, shallow ulcers situated side by side in the posterior wall of its first part. In the second part of the duodenum there was a diverticulum placed medial to and above the ampulla of Vater, and separated from the latter by only a thin mucous fold

(*Fig.* 231). Of oval shape and 0·5 cm. in its greatest diameter, the ostium gave into a sac 2·6 cm. in depth and with a maximum diameter of 2 cm. Passing upwards and medially into the head of the pancreas, this sac lay posterior to the common bile and pancreatic ducts, with both of which it was in close contact. Very thin-walled and extremely expansile, it was lined by a mucous membrane which was thrown into several folds, the most marked being a diaphragm-like flap near the ostium. The sac was filled with brownish fluid.

The pancreas was moderately atrophied and unusually tough, and on section consisted of a relatively narrow layer of tissue in which thickening of the interlobular septa was a feature. The pancreatic duct was grossly dilated along its entire length and in circumference measured 4 cm. in the head and 2 cm. in the tail. Distinctly sacculated in structure, it was lined by a mucous membrane of normal colour and opened with the common bile-duct into a recess-type of ampulla. The accessory pancreatic duct was not located.

The liver was of average size, shape, and consistence, and on section showed a mottled and definitely bile-stained surface in which the small bile-ducts were seen to be dilated. Dilatation also affected both hepatic ducts, the common bile-duct and the cystic duct, which

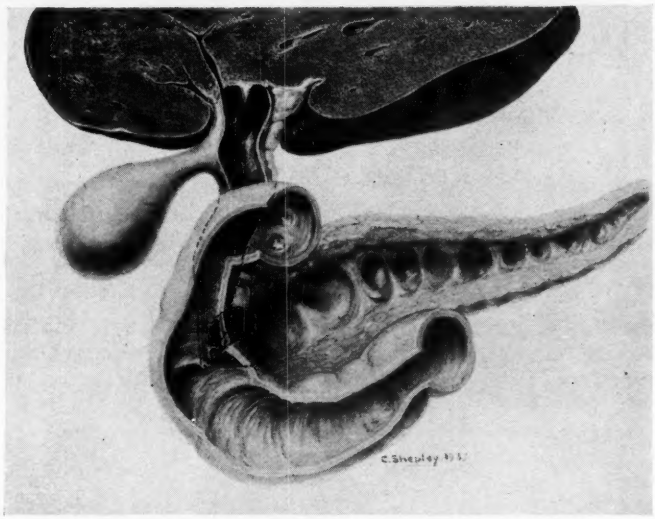

FIG. 231.—*Case* 1. In the second part of the duodenum there is a diverticulum, the ostium of which is situated immediately above and medial to the ampulla of Vater. The pancreatic duct is grossly dilated and marked distension also affects the common bile and cystic ducts and the gall-bladder. The pancreas is atrophied and the liver shows chronic venous congestion. (*From a coloured illustration.*)

respectively measured in circumference 1·5 cm., 5 cm., and 2 cm. Similarly, the gall-bladder was markedly distended and unusually thin-walled. Lined by a healthy mucosa, it was filled with dark green bile, but contained no gall-stones.

The other organs displayed no features requiring mention.

Microscopical.—The *pancreas* showed similar changes in all regions. The interlobular septa were thickened, congested, and œdematous. From many of them narrow fibrous bands passed into the lobules and divided them into islands of variable size. The interlobular ducts, and more especially the intralobular tributaries of these channels, were dilated and lined by flattened epithelium (*Fig.* 232). Both types of duct sometimes contained inspissated secretion in the form of small, hyaline, acidophil masses or concentrically laminated bodies like corpora amylacea. In none of the ducts was there any transitional hyperplasia (Rich and Duff, 1936).

The vast majority of the acini showed widening of their lumen and flattening of their lining cells. Sometimes these changes were accompanied by an increase in the diameter of the acini, and then the enlargement of the lumen could be attributed in at least some measure to obstruction and active dilatation. But, as a rule, no increase in diameter was obvious, and in effecting enlargement of the lumina simple atrophy of the lining cells then appeared to be the important factor. The atrophied acini were more or less devoid of

zymogen granules, while between them there were increased amounts of fibrous tissue. The islands of Langerhans were normal.

The *liver* showed chronic venous congestion. Throughout each lobule, but chiefly in its inner half, a proportion of the liver cells and bile canaliculi contained granules or small

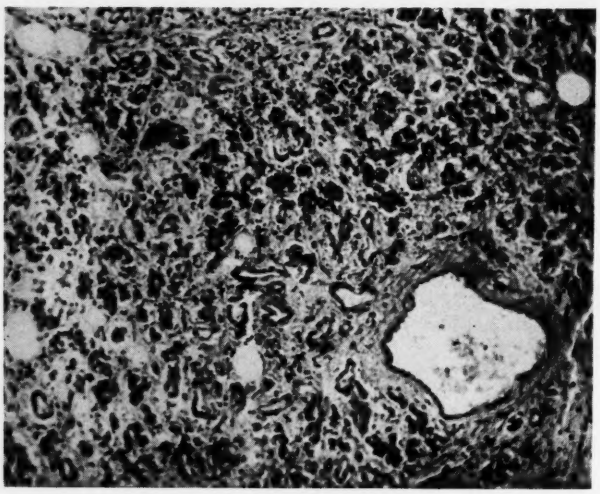

FIG. 232.—*Case* 1. *Pancreas*: The interlobular duct at the bottom right is dilated and lined by flattened epithelium. Several small intralobular ducts also show distension and flattening of their epithelium. The acinar tissue is atrophied and partly replaced by fibrous tissue. (H. & E.) (× 75.)

masses of inspissated bile-pigment. Many of the Kupffer cells were also swollen with bile-pigment. Almost without exception, the small bile-ducts in the portal tracts were dilated and lined by flattened epithelium, while their lumina contained inspissated bile and occasional

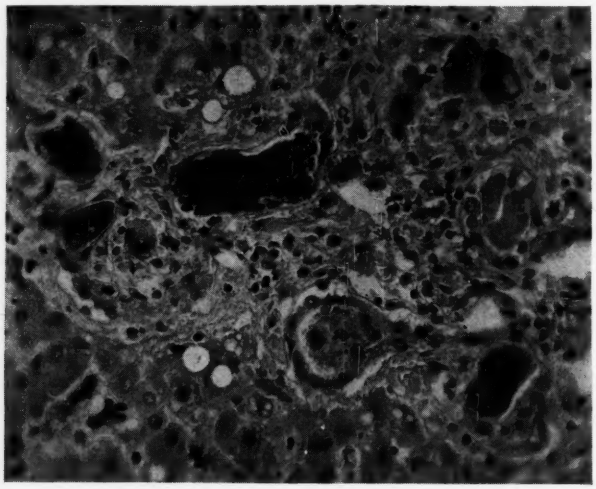

FIG. 233.—*Case* 1. *Liver*: In the portal tract illustrated the bile-ducts are dilated, lined by flattened epithelium, and filled with inspissated bile. Some fatty infiltration is present in the neighbouring liver cells. (H. & E.) (× 240.)

polymorphs (*Fig.* 233). In addition, the portal tracts were excessively infiltrated with round cells, amongst which were some polymorphs. The outstanding feature in the liver was thus dilatation of the biliary system.

The other organs were devoid of interest.

Case 2.—

CLINICAL HISTORY.—For two years, a married woman, aged 73, had experienced occasional attacks of abdominal discomfort unrelated to meals and never severe in type, but accompanied by jaundice. Five hours before being admitted to hospital, the patient was seized with sudden, severe, upper abdominal pain followed by vomiting. On admission she was collapsed and pale, but not jaundiced. She showed no evidence of recent loss of weight. Her pulse was 76 and of poor volume, her temperature 97° F., and her respirations 36. The abdomen was boarded and acutely tender in its upper half, but only slightly rigid and tender below the level of the umbilicus. When the abdomen was opened under anæsthesia, some brownish fluid was found in the upper abdomen and lesser sac, while small areas of necrosis were observed in the fat of the gastro-hepatic omentum and hepatorenal recess. Through an opening in the gastrocolic omentum the pancreas was palpated, but found to be of average

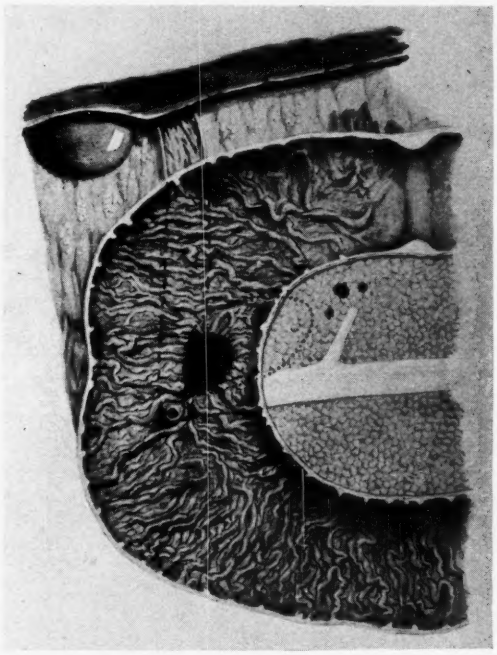

FIG. 234.—*Case* 2. In the second part of the duodenum there is a diverticulum, the ostium of which is placed immediately above and medial to the ampulla of Vater. The pancreatic duct is dilated, but the common bile-duct and gall-bladder are normal. The upper part of the head of the pancreas shows three small areas of hæmorrhage and in the lesser omentum there are numerous foci of fat necrosis. (*From a coloured illustration.*)

consistence. Stomach, duodenum, and gall-bladder appeared normal. The areas of fat necrosis indicated that the case was probably one of acute pancreatic necrosis. The abdomen was, therefore, closed in layers and without drainage. The patient died 14 hours later.

POST-MORTEM EXAMINATION.—

Macroscopical.—The body was that of a well-nourished, elderly female. When the abdomen was opened, several patches of fat necrosis were noted in the neighbourhood of the head of the pancreas, in the lesser omentum, and also low down in the right flank.

Examination of the duodenum revealed a diverticulum with its circular ostium, 2·5 cm. in diameter, situated 0·5 cm. above and medial to the ampulla of Vater (*Fig.* 234). Flask-like in shape, the diverticulum was 5 cm. deep and 4·5 cm. broad, and passed upwards, medially, and slightly dorsally, so that the head of the pancreas lay superior, medial, and anterior to it, and the common bile-duct posterolateral. The sac was very thin-walled and distensible, lined by a mucous membrane which was thrown into a series of folds, and filled with liquid, brown, fæcal material.

The pancreas was of average size, shape, and consistence. Several patches of fat necrosis were present on its anterior surface, and, on section, the head of the organ showed œdema and two or three small areas of hæmorrhage. Together with the common bile-duct, the main pancreatic duct opened into a well-formed ampulla, at the exit of which there was no definable sphincter of Oddi. The pancreatic duct was dilated to the extent of measuring 2 cm. in circumference, while its mucous lining was normal. The accessory pancreatic duct

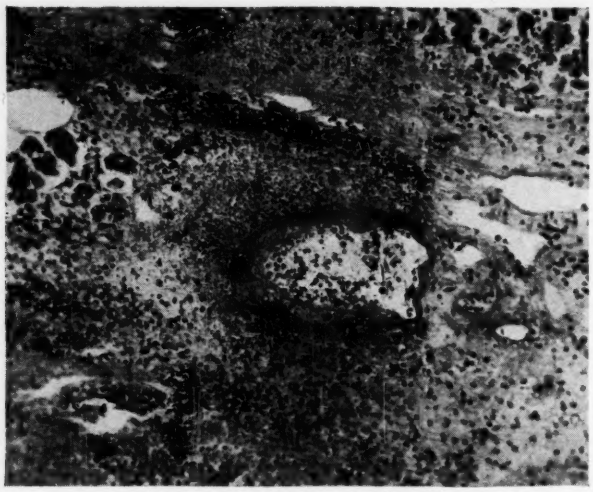

FIG. 235.—*Case* 2. *Pancreas*: The interlobular vessel at the centre is in great part swollen, hyaline, and necrotic, while around it the fibrous and glandular tissues are œdematous and infiltrated with leucocytes and blood. (H. & E.) (× 110.)

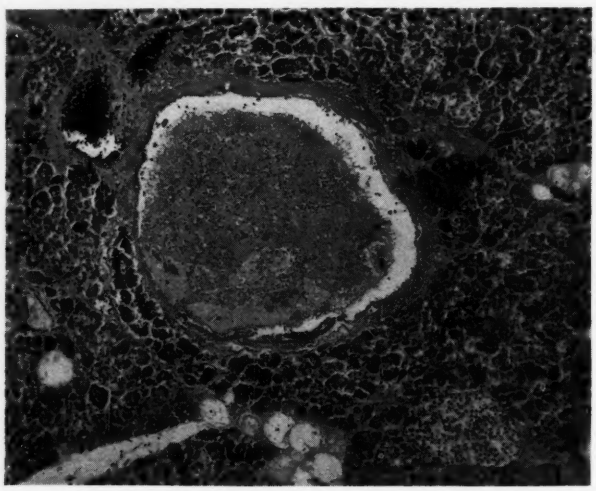

FIG. 236.—*Case* 2. *Pancreas*: The interlobular duct at the centre is distended, lined by flattened epithelium and filled with retained secretion in which are some desquamated cells and many polymorphs. (H. & E.) (× 60.)

was traced horizontally through the head and found to end blindly about 0·5 cm. from the lumen of the duodenum at a level 3 cm. proximal to the opening of the diverticulum.

The other organs exhibited no features worthy of description.

Microscopical.—The *pancreas* showed changes in its head, body, and tail, but principally in its head. These changes involved the interlobular tracts and not infrequently the adjacent acinar tissue also. In the interlobular tracts some of the arteries and veins were necrotic (*Fig.* 235). The lumen of such necrotic vessels occasionally contained fibrin, and sometimes

blood could be seen infiltrating their wall and extending out into the neighbouring tissues. Mixed with this blood there were not infrequently fibrin, serous fluid, and polymorphs. While the majority of them were normal, the interlobular ducts were frequently dilated and lined by flattened epithelium (*Fig.* 236). Some of these distended channels contained inspissated secretion, mixed with which there were occasionally desquamated lining cells and polymorphs and in the fibrous tissue supporting a few of them another feature was a slight infiltration with round cells. None of the ducts showed any evidence of the hyperplastic metaplasia described by Rich and Duff (1936).

In the neighbourhood of the necrotic blood-vessels both acinar and fatty tissues were extensively degenerated. In the case of the acinar tissue, the gland-cells showed loss of their zymogen granules and nuclei, and, finally, complete disintegration into acidophil debris. Mingled with this material were quantities of free blood and polymorphs. In regions at one time occupied by adipose tissue, the changes were those of fat necrosis.

An occasional intralobular duct was slightly dilated and lined by somewhat flattened epithelium, while in its lumen there were sometimes one or two polymorphs. But the vast majority of such ducts were of average calibre and lined by epithelium of normal size. Similarly, apart from the necrotic areas described, the acini composing the secreting parenchyma were normal, while the islands of Langerhans showed nothing unusual. Briefly, the features in the pancreas were thus indicative of (1) duct obstruction, and (2) acute pancreatic necrosis.

The other organs displayed no features of note.

Case 3.—

CLINICAL HISTORY.—The patient was a sparely nourished man, aged 34. For eighteen months he had suffered from diabetes mellitus, but of late he had been very haphazard about his diet and insulin. During the forenoon of the day before coming into hospital, he felt in the upper part of his abdomen a pain which rapidly became worse after lunch and which in the evening caused him to vomit. In hospital, next day, his breath was found to be heavy with acetone and his urine to contain sugar + + +, acetone +, albumin + +, and numerous granular casts. His abdomen did not move on respiration and was rigid and tender generally, but particularly in the epigastrium. His temperature was 99° F., and his pulse 125 per minute. No operative interference being considered feasible, the patient was treated palliatively, and died four days later.

POST-MORTEM EXAMINATION.—

Macroscopical.—The body was that of a sparely nourished, young adult male. A diverticulum was present in the second part of the duodenum (*Fig.* 237). About 0·5 cm. in diameter, its ostium was situated 0·5 cm. above and medial to the ampulla of Vater and gave into a sac 1·75 cm. in depth. The sac was thin-walled, expansile, and lined by a healthy mucous membrane. It consisted of a large lateral recess and a smaller medial one, so that, as a whole, the diverticulum had a bicornuate appearance. The larger horn was placed medial and posterior to the common bile-duct, from which it was separated by tissue about 1 mm. in thickness, while the smaller horn was related inferiorly to the pancreatic duct from which it was separated by only a very thin slip of tissue. The sac contained a little brownish fluid.

The pancreas was of normal size and shape, but abnormally firm. Streaks of fat necrosis in the interlobular septa were found in all regions from the head to the tail. The interlobular septa also showed congestion as well as localized hæmorrhages, both old and recent. The pancreatic duct was of normal size and lined by a healthy mucosa. No accessory duct could be located. The fat enveloping the pancreas was stippled with small patches of necrosis, but there was no evidence of peritonitis.

The other organs were devoid of any noteworthy feature.

Microscopical.—The *pancreas* showed similar changes in its head, body, and tail. Even in the least affected regions of its interlobular tracts the small vessels were congested, while the fibrous and fatty tissues were in some degree infiltrated with polymorphs, lymphocytes, and plasma and foamy cells. In the more affected regions the outstanding change was fat necrosis (*Fig.* 238). Occasionally the necrotic fatty tissue was infiltrated with blood, but more often the infiltrating cell was the polymorph or foamy cell, while mixed with or apart from these cells there were sometimes considerable amounts of fibrin. A few of the arteries and veins in the interlobular tracts were necrotic, and both adjacent to and away from degenerated fat and vessels, occasional small areas of acinar tissue also showed necrosis.

Many of the interlobular ducts were dilated and lined by flattened epithelium (*Figs.* 239, 240). In the lumen of such dilated channels there were sometimes quantities of inspissated secretion and occasionally desquamated lining cells. None of the ducts showed

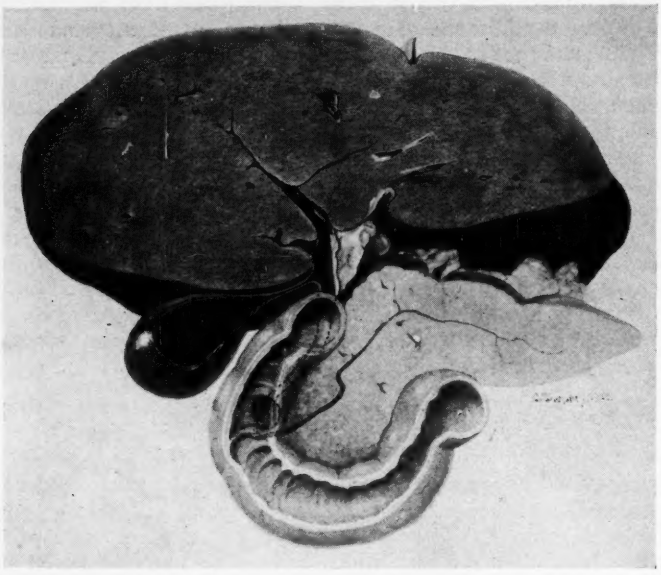

FIG. 237.—*Case* 3. In the second part of the duodenum there is a diverticulum, the ostium of which is situated immediately above and medial to the ampulla of Vater. The pancreatic and common bile-ducts and the gall-bladder are of normal dimensions. Pale streaks of fat necrosis are present throughout the pancreas and in the fat along its upper border, while in the body of the pancreas there are also several dark lines of hæmorrhage. (*From a coloured illustration.*)

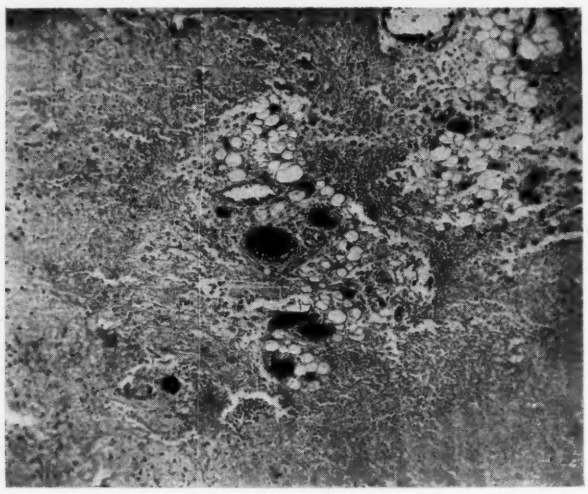

FIG. 238.—*Case* 3. *Pancreas*: In the centre and at the top right there are small areas of congested adipose tissue. Elsewhere the fat has undergone necrosis and has been replaced by granular debris. (H. & E.) (× 50.)

any of the transitional hyperplasia described by Rich and Duff (1936). Like the channels into which they led, the intralobular ducts were often dilated and lined by flattened epithelium. They also contained small amounts of inspissated secretion and occasional desquamated cells.

The glandular tissue was universally involved, but more so in some parts than in others. The changes affecting the acini included flattening of their epithelial cells and enlargement of their lumen. In some cases, enlargement of the lumen was explicable wholly on the grounds of atrophy of the lining cells, but in many other instances the enlargement was

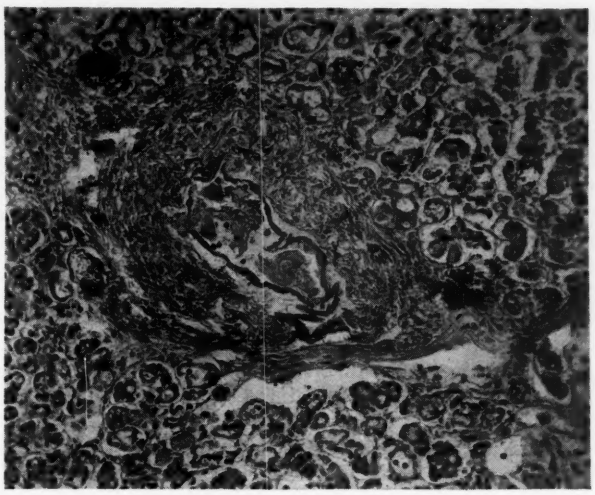

FIG. 239.—*Case* 3. *Pancreas*: The interlobular duct to left of the centre is dilated and lined by flattened epithelium. Both in the secretion within the duct and in the œdematous periductal stroma there are a few inflammatory cells. In the neighbourhood many of the acini show flattening of their epithelium, and while of these some are shrunken, others are dilated. (H. & E.) (× 90.)

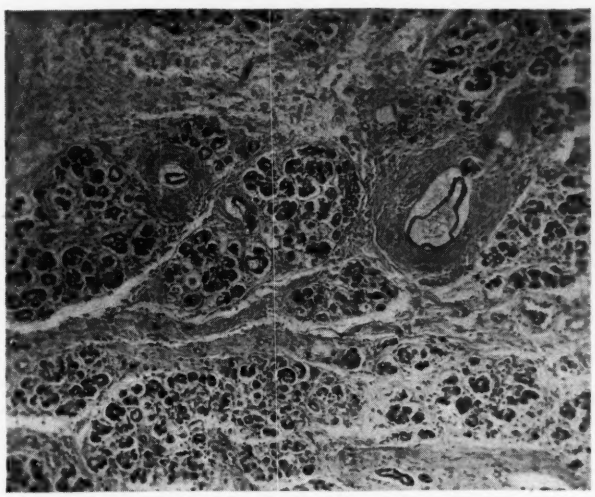

FIG. 240.—*Case* 3. *Pancreas*: The interlobular duct to the right of the centre is distended and lined by definitely flattened epithelium. The acinar tissue shows atrophy and has to a considerable extent been replaced by intersecting bands of fibrous tissue. (H. & E.) (× 55.)

considerable and accompanied by an actual increase in the diameter of the glands. In acini of the latter type, it was justifiable to conclude that in effecting enlargement of the lumen two factors had been at work, namely, simple atrophy of the lining cells and an active dilatation of the glands, the result of increased intra-acinar pressure. Final disappearance of the secreting parenchyma had been followed by an overgrowth of fibrous tissue both around and within the lobules. The new fibrous tissue was loose and œdematous and

infiltrated with polymorphs, lymphocytes, plasma cells, and foamy cells in small numbers. Of the islands of Langerhans, about half were hyaline.

The other organs were without any features of importance.

Case 4.—

CLINICAL HISTORY.—For some years, a married woman, aged 46, had been subject after meals to attacks of abdominal discomfort, flatulence, and occasionally vomiting. About 7 a.m. on the day of admission, she experienced a particularly severe attack of such discomfort and flatulence. At 1 p.m. she was struck down by a sudden, agonizing pain felt at first in the epigastrium, but later over the entire abdomen, and subsequently she vomited several times. After her admission to hospital at 7 p.m., examination revealed abdominal rigidity and tenderness widespread in distribution, but most marked in the epigastrium. There was an absence of abdominal breathing and the liver dullness was diminished. Her face was grey and her extremities cold. Her radial pulse was impalpable and her temperature was 100·8° F. Morphia and digitalin were administered, but her pulse did not improve and without having been operated upon she died nine hours after admission.

POST-MORTEM EXAMINATION.—

Macroscopical.—The body was that of a well-nourished, middle-aged female. The abdominal cavity contained about 200 c.c. of clear, brownish fluid. The duodenum in its second part showed a very thin walled diverticulum. Circular in shape, with a diameter of 0·5 cm., the ostium of this sac was situated immediately medial to the ampulla of Vater and opened into a cavity of spherical form with a diameter of 3 cm. The lateral half of the diverticulum was situated posterior to the lower end of the common bile-duct, while its medial half lay posterior to and above the termination of the pancreatic duct. Completely filling the lumen of the diverticulum there was a stone of brownish-yellow colour and relatively soft consistence. It was composed of alternating layers of yellow and brown material, together with a small amount of fibrous substance, and chemically it was composed of a mixture of cholesterol and fæcal matter. The duodenal mucosa was normal in appearance.

The pancreas was swollen and soft, and in its head, body, and tail there were areas of hæmorrhage. This hæmorrhage was more or less restricted to the interlobular septa, and in consequence the lobules tended to be unusually well defined. In all regions of the organ, particularly its head, there were also patches of fat necrosis, and further foci of the same condition were found in the fat of the lesser peritoneal sac. The main pancreatic duct was dissected out along its whole length and found to be normal in both calibre and appearance.

The liver weighed 1232 g. and was pale and soft. The gall-bladder was of average dimensions. It was lined by a healthy mucosa and contained no gall-stones. The cystic duct was normal in calibre, but the common bile-duct was dilated to the extent of being 2 cm. in circumference along its entire length. Both ducts were lined by healthy mucous membrane.

The other organs exhibited no feature of particular interest.

Microscopical.—All the blocks of tissue taken for examination were so autolysed as to be useless for descriptive purposes.

DISCUSSION

Since the publications of Odgers (1929) and Edwards (1935), duodenal diverticula have generally been classified as primary, secondary, and vaterine. In each of the cases reported above, the diverticulum exhibited the characteristics of the primary type. As a result of both post-mortem (Baldwin, 1911; Linsmayer, 1914; Nagel, 1925; Horton and Mueller, 1932; Grant, 1935) and radiological (Case, 1920; Cole and Roberts, 1920; Andrews, 1921; Spriggs and Marxer, 1925; Cryderman, 1927; Larimore and Graham, 1927; Lemmel, 1934; Wheeler, 1938; Edwards, 1939) investigations, primary diverticula of the duodenum are now recognized as being of relatively common occurrence. Experience has shown that despite this frequency they are, nevertheless, seldom associated with pathological affections, either of their own structure or of neighbouring organs. Indeed, the earliest authors (*see* Baldwin, 1911) regarded them as anatomical curiosities with

no clinical significance. Bassett (1907) and Rosenthal (1908) were the first to indicate that this was not absolutely true, and that occasionally duodenal diverticula could apparently lead to dangerous and even fatal complications. By radiological methods in 1913, Case (1916) demonstrated the existence of a duodenal diverticulum during life, and from this it was only a step to excision of the abnormality, as first reported by Forssell and Key (1915), Stewart (1916), Basch (1917), and Ritchie and McWhorter (1917). Since then, the combined observations of post-mortem, radiological, and operative experience have led to a much increased understanding of duodenal diverticula, particularly regarding the complications to which they are subject or to which they may give rise.

COMPLICATIONS OF DUODENAL DIVERTICULA

These complications may be detailed as follows :—

1. Obstruction.—

a. Obstruction of Duodenum.—Of this sequel, the following examples have been recovered from the literature. According to Bauer (1912), a male, aged 52, had suffered from projectile vomiting two or three hours after meals. Post mortem the stomach was found to be very dilated and in the duodenum there were two perivaterine diverticula, of which the larger had compressed the more proximal duodenum. Basch (1917) recorded the case of a female, aged 36, who had complained of heartburn, flatulence, and an aching pain in the right upper abdomen. These symptoms were found by X rays and at operation to be due to a large diverticulum which took origin from the duodenum at the angle between its second and third parts. The second portion of the duodenum was markedly hypertrophied and dilated, while the third portion was normal in size. Jacquelin and Quénu (1927) reported the case of a female, aged 54, who had experienced attacks of abdominal pain, vomiting, and diarrhœa. Diagnosed radiologically and confirmed operatively, a diverticulum about 8 cm. long was found with its stoma situated just proximal to the duodenojejunal junction and its fundus presenting between the gall-bladder and the duodenal bulb. Resection of the diverticulum effected a complete disappearance of symptoms and a return of the duodenum to its normal shape and position. Cromie (1933) related how a female, aged 38, had experienced a stabbing epigastric pain which came on immediately after food and which was relieved by vomiting. By X rays there was diagnosed a diverticulum of the fourth part of the duodenum, and at operation a pouch was found in this situation and excised. Cromie suggested that the vomiting which ceased with the operation was caused mechanically by pressure of the pouch on the duodenum.

b. Obstruction of Common Bile-duct.—In an autopsy on a male, aged 45, Marie (1899) found two duodenal diverticula, of which the larger was perivaterine and lay immediately behind the second part of the duodenum. Simultaneously, the common bile-duct was dilated. This dilatation of the bile-duct Marie considered to be congenital, but the probability is that it was a pressure-effect of the perivaterine diverticulum. Rosenthal (1908) recorded the case of a female, aged 70, who developed increasing jaundice and died. Autopsy revealed an inflamed diverticulum of the perivaterine type, a dilated common bile-duct, and areas of fat necrosis on and in the pancreas. According to Bauer (1912), a female of 80 became jaundiced and died. Autopsy showed that associated with a dilated condition of the bile-ducts and gall-bladder there was a diverticulum which arose some

centimetres distal to the ampulla of Vater. Wilkie (1913) published two similar cases. A male, aged 58, was seized with abdominal pain, rapidly became collapsed, and died sixteen hours after the onset of his illness. Autopsy revealed a large diverticulum about 2·5 cm. above the ampulla of Vater, dilatation of both common bile and pancreatic ducts, and evidence of acute pancreatic necrosis. Post mortem a female, aged 47, showed a perivaterine diverticulum in immediate lateral relationship to a dilated common bile-duct. Bell (1921) described two cases in neither of which were there any symptoms referable to the diverticulum. In one, a male, aged 42, a perivaterine diverticulum was associated with a slightly dilated common bile-duct. In the other, a male, aged 61, there were two duodenal diverticula, of which the more proximal amounted to a dilatation of the ampulla and lay in front of a moderately dilated common bile-duct. Bengolea (1928) described the case of a female, aged 46, who had experienced two attacks of painless, afebrile jaundice. Radiological examination revealed a calculus in the gall-bladder and a perivaterine diverticulum. At operation, a distended gall-bladder was removed and the common bile-duct found to be free of gall-stones, yet two months later jaundice reappeared and was attributed to obstruction of the bile-duct by the diverticulum. Odgers (1929) drew attention to the presence in the Royal College of Surgeons' Museum (London) of a pouch 2 cm. above the biliary papilla in association with which there was some dilatation of both common and cystic ducts. Nicholson (1935) recorded the case of a male, aged 66, who complained of epigastric discomfort and severe jaundice. Post mortem, a duodenal diverticulum was found firmly attached by fibrous adhesions to the common duct and duodenum. The common and cystic ducts were dilated, but the condition of these channels was overshadowed by an enormous enlargement of the gall-bladder, which actually held 300 c.c. of dark green bile.

Evidence of interference with the bile-passages occurred in *Cases* 1, 2, and 4 of the series above reported. In *Case* 1, a male aged 69 was admitted to hospital with the symptoms and signs of obstructive jaundice. Post mortem the abnormalities found were a typical perivaterine diverticulum and a markedly dilated condition of all the biliary passages. Indeed, the degree of dilatation of the common bile-duct in this case is the greatest ever recorded as having been produced by a diverticulum of the duodenum. In *Case* 2, a woman of 73 had for two years experienced attacks of abdominal discomfort and jaundice. She died from acute pancreatic necrosis. Post-mortem examination revealed a perivaterine diverticulum, but no abnormality of the biliary passages. Nevertheless, the dilated condition of the pancreatic duct suggested that the jaundice had been due to temporary obstruction of the common bile-duct by the diverticulum. In *Case* 4, a woman of 46 had been subject after meals to attacks of abdominal discomfort and vomiting. After death from acute pancreatic necrosis, autopsy showed a perivaterine diverticulum and dilatation of the common bile-duct.

c. Obstruction of Pancreatic Duct.—Case 1 was remarkable not only for a grossly dilated biliary system, but also for the markedly distended state of the main pancreatic duct and its tributaries. Dilatation of the duct of Wirsung is uncommon, and both in my experience and in the literature the case is unique in that it presents such an extreme example of this abnormality.

Cases 2, 3, and 4 were similar inasmuch as each was characterized by a perivaterine diverticulum and acute pancreatic necrosis. *Cases* 2 and 3 showed

additional resemblance in that the ducts of the pancreas were in each case dilated and lined by flattened epithelium. In *Case* 2 this dilatation affected principally the main duct and its interlobular tributaries, while the intralobular twigs were affected in less measure. *Case* 3 had a main duct of normal calibre, but both inter- and intralobular ducts were considerably dilated. Indicative of obstruction, this distension of the pancreatic ducts is explicable as a pressure effect of the diverticulum which was present in each instance at the exit of the main pancreatic duct. It is thus obvious that in both *Case* 2 and *Case* 3 the occurrence of acute pancreatic necrosis was preceded by obstructive dilatation of the ducts of the pancreas and, therefore, by a definite increase in the pancreatic intraductal pressure. In *Case* 4 the main duct was of average calibre, but, as proved by microscopical examination of *Case* 3, such a finding by no means excludes possible dilatation of the lesser ducts. Autolysis of the tissue prevented the determination of such a state, but the fact that the common bile-duct was dilated suggests that in this case there may also have been some obstruction of the pancreatic duct.

A review of the literature reveals that the association of a perivaterine diverticulum and acute pancreatic necrosis has been reported several times. According to Bassett (1907), a male aged 78 was admitted to hospital with a sacral abscess and later died from exhaustion. Post mortem, hæmorrhage and necrosis were found in the head of the pancreas as well as necrosis in the fat both within and around the pancreas. The main pancreatic duct and its branches were dilated, while the glandular tissue showed fibrotic atrophy. In the duodenum a short distance proximal and medial to the ampulla of Vater, there was a diverticulum the wall of which was inflamed and hæmorrhagic. Normal in size, the gall-bladder and bile-ducts were free of stones. As mentioned, Rosenthal (1908) recorded the case of an elderly female who developed jaundice and died. Autopsy revealed an inflamed diverticulum of the perivaterine type, and although the pancreatic duct was normal in calibre, areas of fat necrosis were found both in and on the pancreas. The first of the series of duodenal diverticula reported by Wilkie (1913) is also an example of the association. A male, aged 58, was seized with abdominal pain and died sixteen hours later. Autopsy showed a large diverticulum, the stoma of which was situated on the inner aspect of the duodenum about 2·5 cm. above the ampulla of Vater. The main pancreatic duct was dilated and there were hæmorrhage and necrosis in the pancreas as well as fat necrosis both around the pancreas and in the omenta. Molesworth (1929) described how a male aged 45 had had three attacks of severe abdominal pain. Post mortem, the terminal 4 cm. of the pancreas were necrotic and hæmorrhagic, while some focal necrosis was present in the neighbouring fat. About 2 cm. distal to the ampulla a duodenal diverticulum burrowed into the pancreas. The gall-bladder contained three small calculi, but the common bile-duct which opened with the duct of Wirsung was free of stones. Rich and Duff (1936) recorded another relevant case. Besides the features of acute pancreatic necrosis, autopsy on a male aged 64 showed a duodenal diverticulum in the head of the pancreas and obstruction of the main pancreatic duct as well as dilatation of the ductules and acini in the pancreas.

From the literature there have thus been gathered 5 examples of associated perivaterine diverticulum and pancreatic necrosis. Moreover, in the four of these cases in which its condition is mentioned the pancreatic duct is described as being normal in one and dilated in three. In these three cases, it is, therefore, justifiable

to conclude that throughout the duct system of the pancreas there existed a state of raised pressure prior to the occurrence of the acute hæmorrhagic lesion. The same conclusion regarding intraductal pressure was justifiable in two of the three cases of pancreatic necrosis reported above. Considering the combined group of 7 cases in which the condition of the ducts was investigated, 5 thus exhibit the common factor of a raised intraductal pressure, while in the remaining cases the possibility of a similar condition cannot be denied.

Basing their observations upon both post-mortem and experimental material, Rich and Duff (1936) maintain that all the phenomena of acute pancreatic necrosis are explicable on the grounds of an escape of pancreatic juice from the ducts into the surrounding tissues. The tryptic ferment either in the form of already active trypsin or activated trypsinogen then proceeds to produce hyaline necrosis of arteries and veins, with resultant hæmorrhage, and the lipase to split the neutral fat of the adipose-tissue cells, with consequent fat necrosis. An escape of pancreatic juice into the organ can occur only through destruction or rupture of the ducts or acini, and as ways in which this may be brought about, the authors cite the following possibilities : (i) external trauma ; (ii) infarction ; (iii) infection with tissue destruction ; (iv) retrojection of bile into the pancreatic duct with rupture of the acini ; and (v) pressure due to obstruction of ducts from outside the pancreas or within its substance.

Although Drennen (1922), Armstrong (1939), and Adams (1939) have reported cases of pancreatic necrosis associated with violence, *trauma* must be regarded as a rare cause. Rich and Duff (1936) record a case of pancreatic necrosis which was immediately preceded by focal *infarction* of the organ, but, like trauma, such a phenomenon must be regarded as an uncommon factor. That *infection* is a frequent cause of pancreatic necrosis remains so far unproved. Bacteria may spread to the pancreas from various sources and in several ways, e.g., from an infected biliary system via lymphatics or pancreatic duct, from the intestine by the retrojection of infected juice along the duct of Wirsung, or from a distant focus of inflammation by the blood-stream, but spread of infection has been assumed to occur much more often than it has been demonstrated. Moreover, the mere entry of infection into the pancreatic duct will not of itself provoke pancreatic necrosis unless, as an intermediate effect, it leads to disruption of the ducts or acini with liberation of potent tryptic ferment. Since Opie (1901) and Bunting (1906) published cases of pancreatic necrosis in which a gall-stone was found obstructing the ampulla of Vater, the *retrojection of bile* has always been cited as a cause of the disease, but such is a rare occurrence and acts, not by reason of the fact that bile is an irritant or activator, but because it effects rupture of the duct-acinar system. Such a conclusion is supported by the knowledge that not only bile, but several other agents, e.g., gastric juice, acids, alkalis, formaldehyde, etc. (Dragstedt, Haymond, and Ellis, 1934), are capable of producing pancreatic necrosis.

Finally, Rich and Duff maintain that in the majority of cases pancreatic necrosis results from *obstruction* of the duct system of the pancreas. In some cases, this obstruction occurs in relation to the main duct and is due to such factors as a duodenal diverticulum, pancreatic calculus (Rienhoff and Lewis, 1934), and gall-stone in the lower end of the common bile-duct, but in most instances the obstruction is found in tributaries of the duct within the pancreas and takes the form of a proliferative and transitional metaplasia of the lining epithelium. In a review

of the pathogenesis of acute pancreatic necrosis, Cole (1938) also emphasizes the importance of duct obstruction, and to the theory still further support is given by the above eight cases in which pancreatic necrosis was associated with a perivaterine diverticulum, and particularly by those five instances in which evidence of obstruction was afforded by the dilated condition of the ducts and acini.

But in view of the non-occurrence of pancreatic necrosis in *Case* 1, in the not uncommon instances of carcinoma of head of pancreas associated with compression of the main duct, and in many cases of experimental ligature of the pancreatic duct, it must be admitted that duct obstruction does not invariably provoke pancreatic necrosis. In explaining such exceptions, the degree of activity of the secretory glands is probably an important factor, as indicated by two observations: first, Eggers (1924) noted that ligation of the pancreatic duct produced pancreatic necrosis only when performed during active digestion; secondly, pancreatic necrosis often develops shortly after the patient has indulged in a large meal or a bout of alcoholism. In *Case* 2, it may be remembered, the epigastric pain heralding the onset of the disease manifested itself in the forenoon and *became worse after lunch*. The frequency with which obese persons are the subjects of pancreatitis is probably a related observation, in that such individuals tend to eat large meals. The non-occurrence of necrosis in *Case* 1 may thus have been due to the observed fact that the acini were markedly atrophied and thus capable of secreting only small quantities of juice.

2. Diverticulitis.—Toward this complication, the relative immunity of duodenal diverticula is probably dependent upon three factors: (*a*) the sterility of their content; (*b*) their retroperitoneal situation, which permits of ready distension; and (*c*) their inverted position and the usually wide-mouthed character of their ostium, which together tend to effect free drainage into the bowel. On the other hand, it must be remembered that (*a*) as in the first three case reports above, the ostium is often concealed among the plicæ circulares of the duodenum and that (*b*) little or no muscle is present in the sac wall. Taken together these facts suggest that duodenal diverticula, once filled, may not readily empty themselves. Such a conclusion is supported by the fact that, while he found the average emptying time of the sac in 18 consecutive cases to be eleven hours, Case (1920) not uncommonly observed barium being retained beyond forty-eight hours and in one case for seven days. Stagnation of the content of the diverticulum favours bacterial growth, and thus there follow infection of the wall of the diverticulum and diverticulitis.

The rarity of duodenal diverticulitis may be gauged from the small number of recorded cases, and is thrown into still greater relief when contrasted with the frequency of diverticulitis of the ileum and more especially of the colon. Bassett (1907), Rosenthal (1908), and Bauer (1912) were the first to record cases of inflamed duodenal diverticula, and of these accounts have been given. Downes (1922) described how a female, aged 39, complained of upper abdominal pain followed by vomiting, and how at operation there were found springing from the third part of the duodenum two pouches, both of which were proved microscopically to be acutely inflamed. From a female, aged 27, with a history of epigastric pain and vomiting, Huddy (1923) removed a perivaterine diverticulum which showed severe congestion, hæmorrhage, infiltration with acute inflammatory cells, and necrosis. Butler and Ritvo (1925) recorded the case of a male, aged 40, who had suffered from

attacks of epigastric pain, vomiting, and diarrhœa. A diverticulum showing marked inflammatory changes was found springing from the junction between the first and second parts of the duodenum and inversion of the abnormality was followed by complete relief of symptoms. The cases described later under the sequel of peridiverticulitis may naturally be included as examples of diverticulitis. Again, Downes (1922), Maclean (1923, 1927), Lund (1928), and others have recorded cases in which the symptomatology has been suggestive of diverticulitis, but in which the diagnosis was not confirmed by either naked-eye or microscopical evidence.

Diverticulitis may in turn lead to one or other of several sequelæ, but, as a review of the literature shows, all of these are like diverticulitis itself in being rare occurrences :—

a. Perforation.—Monsarrat (1926) recorded the case of a female, aged 58, who developed severe pain below the ribs, and in whom at operation there was found springing by a stalk from the second part of the duodenum a pouch which had perforated at its apex. According to Beaver (1938), a male aged 54 experienced severe abdominal pain and vomited several times. Post mortem a diverticulum was found on each side of the ampulla of Vater; the pouch to the right was acutely inflamed and had ruptured at its apex. Boland (1939) recorded the case of a 59 years' old male who was seized with intense upper abdominal pain and died after a laparotomy. Autopsy revealed a perivaterine diverticulum which had perforated at its apex.

b. Peridiverticulitis.—Case (1916) described the case of a female, aged 45, who had had gastric symptoms for six years and who radiologically was found to have a diverticulum of the third part of the duodenum. So intimately adherent was the pouch to the surrounding pancreatic tissue that its excision proved impossible. Maclean (1927) recorded two relevant cases. A male, aged 37, complained of epigastric pain and was found on radiological examination to have a diverticulum of the fourth part of the duodenum. Operation further revealed the presence of adhesions between the right half of the transverse colon and duodenum. Since no other abnormality was found in the neighbourhood, the adhesions were attributed to involvement of the peritoneum in an inflammatory process taking origin in the diverticulum. A female who complained of epigastric pain was proved by X rays and operation to have a diverticulum of the third part of the duodenum. Simultaneously it was noted that the duodenum was obscured by an "inflammatory veil", the source of which was attributed to the pouch. According to Lucinian (1930), a female aged 36 had complained of epigastric pain unrelated to food; radiological investigation revealed a duodenal diverticulum, and at operation this pouch was found to be perivaterine in position and to be walled off from the head of the pancreas by inflammatory tissue. Nicholson (1935) described how a male of 66 had complained of epigastric discomfort and severe jaundice and how autopsy exposed a perivaterine diverticulum attached by dense fibrous adhesions to the common bile-duct and duodenum.

c. Duodenitis.—This is a rare sequel. As mentioned, Bauer (1912) related how a female, aged 80, developed jaundice and how post mortem a diverticulum occurring some centimetres distal to the ampulla was found in association with an inflamed duodenum covered with mucus. As also quoted, Wilkie (1913) described two cases in which he considered duodenitis to be present. As evidence of such

duodenitis, however, he only mentioned the presence of tenacious mucus coating the duodenum in the first of his cases.

d. Cholangitis.—In the second of his two cases, Bauer (1912) described inflammation of the bile-ducts as a sequel to diverticulosis and diverticulitis of the duodenum, but this is the only instance in which the association is recorded in the literature.

3. Content of Calculi.—

a. Enteroliths.—Although numerous reports of duodenal diverticula are now to be found in the literature, *Case* 4 of this series is the first to describe the presence of a calculus in the duodenal pouch. The reasons for the rarity of calculus formation in such a pouch are probably similar to those preventing the occurrence of diverticulitis. The combined influence of these factors is to effect free drainage into the bowel, and it is, therefore, obvious that the ebb and flow of intestinal content out of and into the pouch in *Case* 4 must have been unusually sluggish.

b. Gall-stones.—In a female of 80, Chomel (1710) discovered a duodenal pouch containing 22 stones. Reviewing this case, which is in effect the first recorded instance of duodenal diverticulosis, Odgers (1929) considered that the pouch was probably a dilated ampulla of Vater and that the stones in it were biliary calculi. Midway between the pylorus and Vater's ampulla in a male, aged 87, Harley (1857) described a diverticulum in which there was a large gall-stone. Since the gall-bladder was thickened and buried in adhesions, it is probable that the diverticulum was actually a traction pouch into which the gall-stone had ulcerated. Operating on a female, aged 49, who had experienced acute pain in the right hypochondrium, Harries (1932) discovered a perivaterine diverticulum in which was a large, annular stone apparently consisting mainly of cholesterol. Harries suggested that the component parts of the stone originated in the gall-bladder and became fused in the diverticulum.

4. Carcinoma.—The only case in which malignancy has occurred in association with a duodenal diverticulum was reported by Morrison and Feldman (1925, 1926). At operation on a man of 59, a diverticulum was found springing from the duodenal cap and at the mouth of this pouch there was a small, indurated carcinoma which had led to secondary invasion of the regional glands and liver. Unfortunately the absence of a post-mortem examination leaves undecided the exact nature of this pouch and its relation to the growth at its entrance.

SUMMARY

Four cases of perivaterine diverticulum are described.

In *Case* 1 the diverticulum produced gross obstruction and dilatation of both the pancreatic and common bile-ducts, with resultant atrophy of the pancreas and death from obstructive jaundice.

In each of *Cases* 2, 3, and 4 the diverticulum was associated with acute pancreatic necrosis.

The aetiology of acute pancreatic necrosis is discussed, and it is shown how *Cases* 2, 3, and 4 favour the view that this disease of the pancreas is obstructive in origin.

The complications of duodenal diverticula are classified as :—

1. Obstruction : (*a*) Duodenum ; (*b*) Common bile-duct ; and (*c*) Pancreatic duct.

2. Diverticulitis, of which the possible sequelæ are: (*a*) Perforation; (*b*) Peridiverticulitis; (*c*) Duodenitis; and (*d*) Cholangitis.

3. Content of calculi: (*a*) Enteroliths; and (*b*) Gall-stones.

4. Carcinoma.

Despite the known frequency of duodenal diverticula as revealed by post-mortem and radiological investigations, these complications are rare, but examples of each are culled from the literature.

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THE SURGICAL REMOVAL OF FASCIOLA HEPATICA FROM THE COMMON BILE-DUCT

WITH A COMMENTARY UPON THIS INFECTION IN MAN

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Fasciola hepatica is the well-known parasite of 'liver rot' in sheep, and its life history and pathological effects belong to the classics of veterinary science. As far as is known, man appears to be equally as susceptible to infection as is the sheep, but the number of recorded cases in humans, considering the widespread chances of contracting this disease, is extraordinarily small. As Brumpt and Lavier have emphasized, however, in their recent review of the subject, human cases may be more frequent than is generally recognized and, for reasons presently to be stated, may be overlooked. In their survey up to 1928 they had collected 89 cases, and Bürgi (1937), in a review of the whole literature, details some 186, based upon the discovery of eggs in the fæces and by the results of duodenal drainage.

Pathological Changes in the Liver as Observed in Sheep.—The chief changes are in the liver, where the calibre of the bile-ducts is increased considerably and the walls show proliferation of the epithelium, forming papillomata. Outside the ducts there is an area of inflammation and an accumulation of eosinophil cells. Sometimes calcified cysts form containing six or more flukes. The inflammation usually spreads to the surrounding hepatic tissue, and in the presence of pyogenic organisms pus formation results.

The liver as a whole usually shows extensive perihepatitis, and cysts may be seen protruding on the surface. The intralobular cirrhosis of the liver may reach a marked degree. In sheep these flukes produce wasting and a severe anæmia, and it is claimed that experienced veterinary surgeons can base their diagnosis on the pallor of the skin alone.

THE INFECTION IN MAN

Course of Infection.—The course of this infection in man, according to Bürgi, Lavier, Bariéty, and Caroli, is characterized by a febrile state with hepatitis, perihepatitis, and pain in the right lower lobe of the liver.

The first phase is associated with the arrival of the immature flukes in the biliary vessels. They are said by some to reach their destination by excysting in the duodenum and migrating up the common duct into the biliary passages, where they grow to maturity. Others, however, think that they burrow through the intestinal wall into the body cavity and so into the liver. When the eggs appear in the fæces the adult stage of the fluke in the biliary vessels is attained; a chronic angiocholitis is produced which may end in a mild degree of cirrhosis. These parasites can persist for a long time (four years or longer) and may give rise to intermittent biliary crises. The prognosis may therefore be serious.

Source of Infection.—In man the source of infection usually appears to be water-cress, because it is eaten raw with vinegar which cannot kill the cercariæ. Usually, of course, it is the wild plant, because in the cultivated variety contamination by sheep excreta is excluded. The chief point in prophylaxis is obviously control and supervision of water-cress beds.

BRITISH CASES FROM THE LITERATURE

The following are details of British cases which have been collected from the literature. The earliest reference is that of Mr. Partridge, quoted by Budd in 1852. He said: "A few years ago a single fluke was discovered post mortem in the gall-bladder of a person who died in the Middlesex Hospital." He was struck with the appearance of the gall-bladder, which, instead of being stained by bile, was perfectly white. Laying it open he discovered the fluke, which was examined by Professor Owen.

C. Fox, quoted by Küchenmeister (1857), abstracted a fully grown *F. hepatica* from a pimple behind the ear of a 39-year-old sailor, but he had previously sailed for many years in the West Indies, the Mediterranean, and in South America.

A more doubtful instance was that of J. Penn Harris, reported by Lankester, who found six flukes in the cloth used by the mother for dressing an abscess of the scalp in her 25-months'-old child in Liverpool.

C. Murchison in 1877, in her well-known *Clinical Lectures in Diseases of the Liver*, quoted a case in a man of 39 under the care of Dr. J. J. Williams, of Barrow-in-Furness. He was intensely jaundiced, and post mortem one fully adult fluke was discovered in a moderately dilated bile-duct in the interior of the liver. This was an undoubted case of cirrhosis of the liver, but at the same time carcinoma of the duodenum and lymphatics was present.

A. Wilson in 1879, recorded an extremely doubtful instance of the passage of a fluke per anum in a girl of 16 in Edinburgh.

A much more authentic case was that of W. E. Humble and W. V. Lush in 1881. This was noted in a labourer, 52 years of age, who when seen on November 6, 1879, was complaining of vomiting with pain in the upper abdomen, and was thought to be a case of gastric hepatic carcinoma. Fistulous abscesses formed in the neighbourhood of the rectum, and at autopsy twenty-six fully adult flukes were abstracted from the hepatic ducts. The liver weighed 3 lb. He had been in the habit of eating water-cress and this must have constituted the source of infection.

G. R. Ward (1911) described a case in a man of 31 who was admitted to Tunbridge Wells General Hospital in November, 1910. A provisional diagnosis of tuberculous peritonitis had been made. It was found, however, that there was an irregular pyrexia with a leucocytosis of 10–16,000 and an eosinophilia of 37·2 per cent, a moderate anæmia, and changes in the red blood-corpuscles. Eggs of *F. hepatica* were numerous in the fæces. No details were given of the occupation of the patient, or of the manner in which infection was contracted.

S. W. Patterson* (1928) quotes the case which was discovered in Ruthin Castle, North Wales. This was in a man of 43, whose illness commenced in November, 1927, with fever, mild rigors, abdominal discomfort, a leucocytosis of 14,700, and 42 per cent of eosinophils. Eggs of *F. hepatica* were present in the fæces. Treatment consisted of massive salines and intravenous injections of stibosan. Patterson also quotes R. C. Clark, who stated in a personal communication that he had found flukes in the course of an operation for empyema of the gall-bladder. No other details are available. This would appear to be the only instance, previous to the one recorded here, of the discovery and removal of these parasites at a surgical operation.

J. H. Biggart (1937) has described the quite unexpected discovery of twelve adult *Fasciola hepatica* in the bile-ducts of an insane woman who died in the Springfield Asylum, Cupar, Fifeshire. The liver was smaller than normal and weighed 36 oz. The larger bile-ducts were dilated and thickened and in many there was hyperplasia of the epithelial lining. The liver parenchyma showed a marked degree of biliary cirrhosis. The patient had lived in a sheep-rearing district of Fifeshire and probably contracted the infection from eating water-cress, and her mental condition may have played some part in coming into contact with infective material.

* This is apparently the same case as that quoted by D. U. Owen (1928).

The most important résumé upon the whole literature of *F. hepatica* in man is by K. Bürgi (1937). Here details are given of 186 cases; most of these are hepatic, as in the instances already recorded, and there are numerous erratic occurrences in the portal and other veins, in muscles, and in skin tumours. Amongst the curious erratic distributions is halzoun, described by Khouri in Lebanon, a condition due to adhesion of flukes to the wall of the pharynx, which causes œdema and is due to eating raw and infected liver.

TREATMENT

Medical treatment of *F. hepatica* infection in man is in an unsatisfactory state. Thymol and ethereal extracts of *Filix mas* have been given an extensive trial. Distol and arecolin, which are used in veterinary medicine, are found to be too toxic for man. Novarsenobenzol and stovarsol have been used, but have no parasiticidal action. Antimony preparations, such as neostibosan, have been employed by Kouri and Bacigalupo in Cuba. In veterinary surgery carbon tetrachloride and ethyl chloride are recommended.

Emetine, injected intravenously or intramuscularly, has given the most encouraging therapeutic results in man. The dose is 0·03–0·04 g. daily. According to Kouri 3 mg. per kilo body-weight is the correct dosage, i.e., 210 mg. for a man of 70 kilos in doses of 60, 50, 50, 50 mg. on successive days. In one case successfully treated the total amount of emetine hydrochloride injected was 460 mg. or 6·4 mg. per kilo body-weight.

It is also recommended that dyes such as gentian violet and magdala rose should be given a trial, but it is impossible to get them into the body in sufficient concentration to have any harmful effect on the flukes.

A more heroic suggestion is that the parasites can be forced out of the gall-bladder by open surgical drainage over a period of from two to three weeks, and this procedure is especially beneficial when the bile is secondarily infected, and is recommended on these grounds by K. Bürgi.

The following is a résumé of therapeutic measures which have been approved:—

1. Emetine hydrochloride intravenously in 1–4 per cent solution for ten days (0·03–0·04 g. daily).

2. Carbon tetrachloride, 1 c.c. daily by the mouth for five days, repeated on two to four occasions and only in thin and vigorous individuals.

3. Gentian violet in 1 per cent solution intravenously on one to three occasions in doses of 20–30 c.c. at intervals of three days.

Additional measures for anæmia are recommended: iron, arsenic, and blood transfusions.

PERSONAL CASE REPORT

The patient, a woman aged 54, had been an actress, and during the course of her career had toured a great deal in South Wales, but had never been outside the British Isles.

The source of the fluke infection is obscure. It is true that she has always been fond of water-cress all her life, and volunteered the statement that on country walks she has been in the habit of chewing grass, or of "running the blades between her teeth". At 18 years she had a tapeworm; at 29 biliary colic, and had passed gall-stones with great pain. In 1925 biliary colic again recurred, so that in 1932 the gall-bladder was removed by J. W.; it was opaque and thickened and there were two small intramural calculi, but none in the lumen. Subsequent to this operation there succeeded a period of calm, but then pain in the back and in the gall-bladder region re-appeared. Pancreatitis being suspected, the abdomen was again explored by J. W. on November 14, 1939. At this operation some adhesions were found between the duodenum and gall-bladder bed which were easily divided.

The common duct was seen to be considerably dilated and the pancreas appeared normal. The duct was opened and a flattened, folded, and relatively soft object removed from the ampulla ; the duct was carefully explored, but no other foreign bodies could be found. The opening of the duct into the duodenum was fully dilated and the incision in the duct closed. The structure removed from the duct proved to be a fully adult *F. hepatica*, containing eggs, and measuring 23 × 13 mm. (which is slightly shorter than the average given in most text-books).

Whether this was a solitary infection (which is by analogy unlikely), is difficult to determine, as repeated direct examination of the fæces and by concentration methods have failed to reveal any ova in the excreta. At the same time there is no anæmia or leucocytosis and the eosinophil cells number 7 per cent.

Subsequent to the removal of the fluke, the patient, after a quiescent interval, complained of recurring stabbing pains in the epigastrium and of a referred dull sensation in the small of the back.

The complexion remains muddy, with patches of dark pigmentation in the axilla and thighs, but there is no evidence of icterus, or the presence of bilirubin in the urine or serum. Though there is no enlargement of the liver and the lower edge is neither palpable nor tender, yet the general impression conveyed is that there is a moderate degree of cirrhosis of the liver.

In the lack of positive evidence of further infection it becomes extremely difficult to determine whether the symptoms of which she now complains are due to wanderings of other fluke individuals in the biliary ducts.

COMMENT

It is important to note that here we have proven an undoubted case of *F. hepatica* in the common bile-duct removed by surgical operation and yet there exist no external evidences of infection at all—such as a marked eosinophilia or eggs in the fæces.

This leads us to the consideration that many other instances of a like nature may exist in cases of obscure hepatic disease, and therefore more elaborate diagnostic aids, such as complement-deviation and intradermal tests, may have to be evolved to detect them.

With the exception of F. C. Clark's case already quoted, and of which no further details exist, this appears to be the only recorded instance of the surgical removal of *F. hepatica* from the human bile-duct in the medical literature.

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THE USE OF FASCIAL GRAFT IN THE CURE OF INGUINAL HERNIA

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An investigation in 1931 of the literature suggested to the writer that in the majority of the papers on inguinal hernia the high percentage of recurrence after operation constituted a reproach to modern surgery, and the inadequacy of the average follow-up led one to presume that the true recurrence figure might be still higher.

This paper shows the results of a personal consecutive non-selected series of 163 elective (non-strangulated) operations for inguinal hernia with as adequate a follow-up as possible. I have set out to stress the need for fuller after-investigation and to advocate the more extensive use of the fascia lata graft technique.

HISTORICAL

As far back as 1901 McArthur[27] started to use fascia to supplement the methods then in use. He freed one end of a strip from the external oblique aponeurosis, and with it he darned across between the falx inguinale and the inguinal ligament. With a second similar strip, tethered still at one end to the parent external oblique, he closed the incision in that muscle. He published his findings in 1904.

In 1910 Kirschner[20] recorded a number of successes with free flap transplants of fascia lata sutured across the weak posterior wall of the inguinal canal. He claimed for fascia lata its accessibility, abundance, strength, inelasticity, and readiness to heal in when transplanted, and that it could be cut to fit an opening of any shape.

It was in 1921 that Gallie and Lemesurier[14] demonstrated the survival of long free fascial strips (6 or 7 in. by $\frac{1}{4}$ in.), and advocated their use in preference to flaps of fascia. They introduced a special curved, large-eyed needle on which the strip is threaded, and using this material a 'darn' is made across the weak area. This work laid the foundation of the modern graft operation.

METHODS OF TREATMENT

Possible Methods.—

1. *Palliative.*—By truss, etc.
2. *Curative.*—
   - *a.* Removal of sac only.
   - *b.* Bassini's operations and modifications.
   - *c.* Use of fascial graft:
     - i. Animal.
     - ii. Homologous.
     - iii. Autogenous: Strips from external oblique; Strips from fascia lata; Sheet from anterior rectus sheath, fascia lata, etc.
   - *d.* Extraperitoneal intra-abdominal method.
   - *e.* Injection treatment.

a. Removal of Sac Only : No Repair.—The muscles of the inguinal canal are entrusted with their natural task of maintaining the abdominal viscera in situ. This by general agreement is considered ideal in the treatment of the small sac of children.

b. Bassini's Operations and Modifications.—Here the sac is removed, the existing muscles are pulled out of their natural lines and folded across to strengthen this weak area of the anterior abdominal wall. This is still by far the most common operation and has its strong advocates. When first introduced it marked a great advance in the treatment of hernia, but as Ogilvie[28] and others have pointed out the catgut sutures in the falx inguinale or conjoined tendons merely strangulate the fibres of the muscle, destroying their sphincteric value without producing any substitute. Striated muscle, pulled out of place by stitches, either remains displaced and becomes feeble and fatty, or it returns to its original site weakened and ineffective, as Gallie[14] has shown. This is also stressed by Burian.[5]

c. The Use of Fascial Graft.—Grafts from animals or other patients have been used, but are admitted to be less satisfactory than autogenous (Burdick, Gillespie, and Higginbotham[4]). In the autogenous type, after removal of the sac, strips are taken from the external oblique or fascia lata of the thigh, or, as Keynes[19] advocates, sheets of fascia turned down from the anterior layer of the rectus sheath. Flaps from the external oblique aponeurosis (Zimmermann[38]) or upper part of fascia lata (Fleming[12]) are also employed.

The fascia obtained is used to form a tough fibrous diaphragm across the area of weakness without any distortion of the musculature. The author has no personal experience of the use of a sheet of fascia from the inguinal region or anterior layer of the rectus sheath, but in Keynes's hands the latter has proved valuable in large herniæ. In 2 cases of large post-operative ventral hernia success has followed the use, as suggested by Gallie,[13] of a sheet of fascia lata, cut into the shape of a many-tail bandage; this should be of considerable value in very large inguinal herniæ, as Behrend[1] also advocates.

d. The Extraperitoneal Intra-abdominal Method.—This method has been devised by Professor A. K. Henry.[18] Briefly it comprises an abdominal midline extraperitoneal approach, the removal of the sac above and closure also from above of the deep or internal inguinal ring—with fascial grafts if large.

e. The Injection Treatment.—This line of treatment has its advocates, especially in the U.S.A. The writer has no personal experience of its use, but it is not without its limitations and difficulties, nor is it free from complications. It is of interest to note that Slobe,[32] as recently as December, 1938, after comparing a large number of series of results of operations and injections, states that in general surgery remains the method of choice.

Methods Adopted at Start of the Series and Reasons for so doing.—As Max Page[31] has said, the practical surgeon will in the first place wish to know what type of operation is most likely to be effective in producing a lasting cure in the individual case.

In view of the high incidence of the inguinal hernia it might be thought a common standpoint as to the best methods and their effectiveness would have been reached by now. This, however, is by no means the case.

For the Bassini operation and its modifications, which formed the whole or bulk of many series, the recurrence figure appeared to vary from 5 per cent to 30 per

cent, while on the other hand Gallie and Lemesurier[15] published in 1930 a series of cases treated with fascial grafts showing remarkable results: in each inguinal case the hernia was either a large indirect one or, if direct, often recurrent and of unusual size.

The striking contrast between these two sets of figures coupled with the unscientific foundation of the Bassini type of operation decided me to pursue the following line of treatment as consistently as possible over a period, in an effort to assess its true value:—

1. In all herniæ in children up to 16 and young adults with small herniæ and good muscles, the sac only was to be removed and no repair attempted; it is, of course, essential that the sac be removed completely, but otherwise the structures in the region should be disturbed as little as possible.

2. In all other herniæ the sac was to be removed and fascia darned across the gap to form a new fibrous diaphragm. Unless the weak area was unusually large, the strip was to be removed from the external oblique, but in the larger cases from the fascia lata.

Methods finally adopted and reasons for making alterations.—Two main alterations were made fairly early in the series. Firstly, there were three rapid recurrences (*Cases* 35, 48, and 57), in young men under 35 with indirect small or medium herniæ, in which the 'sac only' operation was performed. In none of these cases was there difficulty at operation or any sepsis or other post-operative complication.

The age for this type was therefore reduced to under 17 (an occasional exception has been made, however, in the case of females rather over this age with small sacs).

Secondly, the use of the external oblique graft was gradually dropped. While a simple and quick method, only one strip usually is available if the gap in the external oblique is to be closed subsequently, and this strip it was felt is too short to perform an adequate darn in most cases.

Using the strips from the fascia lata, obtained either by the fasciotome or the open method, an adequate repair can be achieved, there being no practical limit to the number of strips that can be taken.

The decision to abandon this method was accelerated by hearing of a recurrence in seven weeks in *Case* 8 (a young man of 23 with a small indirect hernia).

In addition, *Case* 47, on whom a thigh graft for a left inguinal hernia was performed without recurrence, later, on developing a hernia on the right side, was operated on by another surgeon elsewhere: an external oblique repair was performed, and this was soon followed by a recurrence.

Two minor alterations were adopted in 1935—the adoption of the use of a fasciotome for obtaining fascial strips from the thigh in place of the open method, and from 1937 a fascial introducer devised by Moseley[26] was substituted for the Gallie needles. (Behrend[1] has also adopted a fine-pointed hæmostat or special Holder's forceps in lieu of needles.) These two changes, although facilitating the operating, do not in the least effect, one way or the other, the efficacy of the actual operation on the hernia.

The lines of treatment were therefore modified to:—

1. Herniæ in children up to 16—'sac only' operation, no repair.

2. *All* other herniæ—repair with thigh graft (obtained by fasciotome).

This scheme has been followed with but few exceptions.

Details of the Fascial Graft Operation employed.—There are numerous modifications of Gallie's[14] original operation, but that used in this series follows it very closely.

There are a few points which are perhaps worthy of mention: An incision is made as usual above and parallel to the inguinal ligament, but it should be longer laterally than in the Bassini operation, so as to give a clear view of the lateral edge of the deep or internal inguinal ring and at rather a higher level, so as to allow a comparatively large lower flap of external oblique—these points facilitate the insertion of fascial strips later.

It is an advantage to instruct a nurse strongly to invert the foot and bring it near the edge of the table, and whichever side the hernia may be, I generally use the right thigh, as it is slightly easier to use the fasciotome on this side. (If there are bilateral herniæ, sufficient strips can be cut from one thigh.) If there is a scar or other such contra-indication the left thigh is used.

One does not want to go too near the knee, for the distal part of the fascia lata contains a number of transverse strands—the extent of these varies considerably in different subjects—and these make the taking of strips more difficult and are a common cause of the strip breaking.

It is very important also, that the small blades of the fasciotome be sharpened fairly frequently, otherwise the strip will break.

Having passed the fasciotome up the thigh to the hilt and met the resistance of the muscle, one then gives the instrument a further short jerk and pulls gently on the fascial strip held by Kocher's forceps.

In about 70 per cent of cases this frees the upper end of the strip, which can then be removed: in the remainder the strip remains attached and must be freed with a fine tenotome.

The fascial strips thus obtained are used after the manner advocated by Gallie,[14] except that they are picked up each time (in somewhat the same way that catgut is used with a Reverdin needle) with a special Moseley introducer instead of threading on a Gallie needle.

The first suture is inserted into the inguinal ligament (Poupart's ligament) at its insertion into the pubic spine and, if possible, also picks up the periosteum; this is a very important point as unless care is exercised a weak spot easily occurs here (Behrend[1] also emphasizes this).

It cannot be too strongly stressed, that the objective is a darn across the hole like darning a sock.

It is of value to bandage firmly the whole length of the thigh to prevent subsequent oozing.

The operation can be done under general or spinal anæsthesia, the latter being eminently suitable. In this series the thigh sutures were removed on the 8th and those in the groin on the 10th day. The patient was kept in bed for 20 days, and about 8 weeks elapsed before full heavy work was allowed, but he was encouraged to take increasing walking exercise.

The use of a truss as a 'precaution' is strongly deprecated.

In this series the fasciotome devised by H. A. Small[33] has been used throughout. There are a number of other fasciotomes, and since the termination of the series other types have been tried. That devised by Masson[24] is also a good type.

OBTAINING FOLLOW-UP INFORMATION

The Inadequacy and Resulting Inaccuracy of most Follow-ups.—This point is only too clear in the majority of the series.

There are three main facets to be considered: (1) The percentage of total cases followed. (2) The number of years over which the follow-up was pursued. (3) To what extent personal examination was made.

It will clarify the situation, if these are taken separately.

1. *Percentage of Total Cases Followed-up.*—As will be seen in *Table I*, when considered solely from the point of view of the percentage investigated, even the best of these figures are barely adequate for reasonable accuracy, while the value of those series at the other end is negligible.

Table I.—PERCENTAGE OF TOTAL CASES FOLLOWED-UP

	TOTAL	APPROXIMATE (Per Cent)	PERIOD FOLLOWED
Gibson and Felter, 1930[16]	1,618	4·2	2 yr. or more
Block, 1933[3]	20,000	30·0	2 yr. or more
Fallis, 1936[9]	1,600	50·0	2 yr. or more
Davis, L., 1916[7]	1,500	50·0	1 yr. approximately
Grace and Johnson, 1937[17]	1,032	65·0	At least 1 yr., some up to 10 yr.
Burdick, Gillespie, and Higginbotham, 1937[4]	1,485	68·0	1 yr.
		50·0	5 yr.
Zimmerman, 1938[38]		100·0	1 yr.
		45·0	2 yr.
Page, 1934[31]	295	70·0	5–9 yr.
West, Gibson, and Cupp, 1938[37]	1,048	80·0	Not stated
Erdman, 1923[8]	1,093	89·5	3 mth.–7 yr.
Mathisen, 1938[25]	408	85·0	3 yr. or more

2. *The Length of the Investigation.*—The figures for this item vary greatly. Of Gibson and Felter's[16] follow-up only 4·2 per cent were seen for 2 years, 14 per cent for 1 year, and the vast majority therefore for less than this.

Watson[36] advocates instructing patients to attend every 3 months, but only for 2 years. Gibson and Felter[16] instruct their patients to return for examination in 3 months (indirect cases) or 9 months (direct cases) and subsequently "at any time if he has trouble". It is difficult to set much store on such short investigations. As will be seen from the table above many of the series are but for 2 years, but Erdman[8] with 3 months to 7 years, Burdick, Gillespie, and Higginbotham[4] with 50 per cent for 5 years, and especially Page[31] with 70 per cent for 5 to 9 years are clearly of more value. Mathisen[25] also gives the comparatively good figure of approximately 85 per cent traced for 3 years or more.

3. *Nature of the Investigation.*—As will be mentioned in the next section, there are definite reasons for preferring a personal examination—for choice, by the surgeon who operated or by another surgeon at the same clinic—to a written report for the patient. An examination by another medical man lies approximately midway in value.

In the average series it is clearly impossible for all cases to be seen personally, but the larger the number not seen the lighter weight the series carries.

It is clear that the nature of the population from which the patients are drawn varies considerably. Mathisen,[25] of Oslo, states that, although all recurrences were seen, a very small percentage of total cases were examined; the rest all wrote. Norway is a sparsely populated country, and travel by no means easy.

Many authors do not state the nature of their follow-up methods, and with others like Mathisen[25] the post is mainly employed, but in Page's[31] series examination was carried out in all cases traced (70 per cent of total cases operated on), and Erdman[8] examined 90 per cent as compared with 10 per cent seen by other doctors or replying to postal inquiries.

It is obvious that all these follow-ups, which do not approach the 100 per cent mark and do not extend for a period of years are of little value in assessing the true recurrence rate; for it is true, as Fallis[9] states, that the more complete the follow-up and the longer the period under review, the greater will be the number of published recurrences.

The Difficulties and Dangers of Follow-ups.—There is no doubt that there is a tendency for failures to be seen by other surgeons. This point alone makes a close follow-up of cases imperative, if results are to be of value.

Then again, patients may not know thay have a recurrence, when here is one present, as Fallis[9] and Grace and Johnson[17] point out, while the converse is equally true—some patients think they have a recurrent hernia when none can be found at examination. These points show that Erdman[8] is right, when he states that actual examination of the patient at intervals after operation provides the only absolutely reliable criterion for estimating the percentage of recurrence.

Even when examination is made, the position is not in every case absolutely clear, for on occasion some allowances must be made for a slight degree of bulging and impulse along the structures of the spermatic cord (Erdman).

There may be some doubtful cases, but if in doubt a further examination after a short interval will always show whether there was an incipient hernia or not, as recurrences rapidly grow larger.

Another difficulty is to tell whether a second hernia, say a direct hernia following an operation for an indirect hernia, is to be classed as a recurrence or an entirely new one. There is but one way to count such cases—any hernia in the same groin must be considered for statistical purposes as a recurrence (Burdick, Gillespie, and Higginbotham[4]). Mathisen[25] holds that, as almost all recurrences in his opinion appear under 3 years, any hernia seen after this period should be classed as a new one, not a recurrence. One cannot agree with this.

Finally, there are the usual difficulties common to all lengthy follow-ups and especially the movement of the population—and this is not lessened by the fact that the majority of hernia cases are on the average active, and so mobile, young males. It is difficult for some to be examined owing to moving to a distance, and of course others change their address and cannot be traced.

The Criteria of an Ideal Follow-up.—The follow-up should approach as closely as possible to the 100 per cent mark. Patients should be examined whenever possible by the surgeon (or a colleague at the same hospital); failing this, by another doctor, and only when this is impossible should the reply to a detailed questionnaire be accepted.

Such examination should take place 3 months, 6 months, 1 year, and 2 years after operation, and then approximately every year until at least 5 years have

elapsed, and should preferably, as Fallis[9] suggests, continue throughout the individual's life.

Details as to occupation, ability to follow same after operation, and pain in groin and thigh, should also be recorded.

Follow-up Methods Used by Author.—The inscription "Ὁ βίος βραχύς ἡ δέ τέχνη μακρά" greets the medical student entering St. Bartholomew's Hospital in the City of London. Life is indeed short—and with the complexity of life it is difficult to live up to such an ideal. One can, however, attempt it.

The value of such a continuous follow-up was not fully realized at first.

Most of the cases were seen after operation approximately 2 months and again a few months later, and during the last 2 to 3 years new cases report at more frequent regular intervals after this.

In 1937 all the cases to date were circularized with the questionnaire shown below, and in 1939 and 1940 the vast majority were examined personally at hospitals (or at their homes if necessary) by the author.

QUESTIONNAIRE

Private and Confidential

Certain facts in connexion with ruptures are being investigated as a means of checking and improving treatment.

In order that we may help others, I should be grateful for your replies to the following questions :

1. Have you any pain in the region of the groin scar ? .....
2. Have you any pain in the region of of the thigh scar ? .....
3. Have you noticed any recurrence of the rupture or any swelling in the groin ? .....
4. Have you noticed any swelling in the other groin ? .....
5. Do you wear a truss ? If so, why ? .....
6. Have you had any operation since ? .....
7. Are you satisfied with the result of the operation ? If not, for what reason ? .....

Signed .....

Address .....

.....

Less than 9 per cent (13 cases in all), now living at a distance—one wrote from Shanghai to state, incidentally, that he had passed a medical examination recently, and another from Iowa, U.S.A.—who could not be examined by me, have again filled in the questionnaire ; and in 1 double case the patient was examined by a doctor, who kindly reported to me. Two cases have resisted all endeavours to trace, and a few have been lost after 1 or more years. (Further details are given later in *Table II.*)

This admittedly is not the ideal of perfection, but it is perhaps as near as one can get to this ideal, and for all practical purposes should give a sufficiently true picture of the position.

It is proposed to continue the follow-up.

STATISTICS

The writer's figures are given, analysed, and compared with those in the literature. In every case the unit is the hernia, not the patient (e.g., a patient with a double hernia is counted as 2), and each hernia followed up and analysed separately.

Duration of Follow-up.—Details are given in *Table II*. It should be noted that of those followed up 2 died of intercurrent disease: viz., *Case* 36 twenty months after operation, from phthisis; and *Case* 60 three years after operation, from retroperitoneal neoplasm. In neither case was there any recurrence of the hernia.

Table II.—DURATION OF FOLLOW-UP

CLASS OF HERNIA	OPERATIVE MORTALITY	NEVER TRACED	FOLLOW-UP (NON-RECURRENT HERNIA)								RECURRENCES	TOTAL HERNIÆ
			Months		Years							
			3	6	1	1½	2	3	4	5 or more		
Adult males	1	2	125	124	124	115	108	71	58	46	7	135
Adult females and all children	0	0	28	28	28	26	25	17	11	6	0	28
Total	1	2	153	152	152	141	133	88	69	52	7	163

The reason in most cases for the gap between actual and possible follow-up figures is due to insufficient time having as yet elapsed since operation.

In fact, of the 163 herniæ the whereabouts of the patients are still known in all except 7 cases, and of these 1 was traced for over 4 years, 2 more for over 2 years, and 1 for over a year before touch was lost owing to change of address. Of the remaining 3, 2 were never traced, and the third was lost after the 3-months' examination.

Including then as traced cases operative deaths and recurrences, the percentages of traced herniæ are as follows:—

98 per cent traced for 1 year
86 „ „ „ „ 2 years
59 „ „ „ „ 3 „

It is freely admitted that owing to the number of comparatively recent cases the efficiency of the follow-up is as yet not up to ideal, but up to 1 year it is reasonably good, and will bear comparison with most other series.

Sex Incidence (*Table III*).—It is generally agreed that inguinal hernia is far more common in males than females. The actual female percentage would, however, appear to vary considerably: Fallis[9] gives 1·1 per cent, O'Shea[29] 5·1 per cent, Erdman[8] 5·3 per cent, Gibson and Felter[16] 6·8 per cent, while Mathisen's[25] figure is 11·8 per cent. It is interesting to speculate whether perhaps this may be due to the fact that in the rugged countryside of Norway the women have to do harder and rougher work than in the average community.

Table III.—Sex Incidence

	Numbers			Percentage of Total	
	Male	Female	Total	Male	Female
Adults (17 and over)	135	11	146	92·5	7·5
Children (under 17)	13	4	17	76·5	23·5
Total	148	15	163	90·8	9·2

The writer's percentage seems to be rather higher than the usual figure.

Age Incidence (*Tables IV, V*).—From these tables it will be seen that the commonest age periods, in which patients present themselves for operation are 17–29, and 30–39, 47 per cent being between 17 and 40, but cases are spread fairly evenly throughout life. Since the end of 1938, and of this series, men of 82 and 71 have been successfully operated on.

Table IV.—Average Ages for Different Operations

Operation	Adult Males	All Herniæ	Youngest	Oldest
Thigh graft	44	43·8	17	68
External oblique graft	41	40·5	22	62
Sac only	28·7	20	4	39

Table V.—Age Incidence (All Cases)

Age Groups	Number of Herniæ	Percentage of Total
1–16	15	9
17–29	38	24
30–39	36	23
40–49	23	14
50–59	32	18
60 and over	19	12
Total	163	100

The writer cannot agree with those surgeons who, like Gibson and Felter,[16] would refuse operation to those over 50 except for definite indications such as unusual discomfort or strangulation. No less than 51 herniæ, 30 per cent of all the cases in the series, are in patients over 50, and for these the recurrence rate is under 4 per cent and there was no operative mortality.

Type and Side of Hernia.—Details are shown in *Table VI.* It is clear that the types of herniæ will vary considerably in different series, but broadly speaking the proportion of 7·3 per cent for direct hernia is a good average figure. As to side, in this series the figure 49·5 per cent for right-sided herniæ does not agree with the usually accepted statement that there is a slight

preponderance of right over left. O'Shea[29] and Mathisen[25] give 56·8 per cent and 55 per cent respectively. It is possible, however, this may be due to the comparatively small total number of cases in the writer's series.

Table VI.—Type and Side of Hernia (All Cases)*

Types	Right	Left	Total	Percentage of Right-sided
Indirect primary	73	77	150	—
Indirect recurrent	1	—	1	—
Total	74	77	151	48 per cent
Direct primary	1	3	4	—
Direct recurrent	6	2	8	—
Total	7	5	12	58 per cent
Grand Total	81	82	163	49·5 per cent

* There were 18 bilateral cases.

Anæsthesia (*Table VII*).—In this series no operations were performed under local anæsthesia. This type of anæsthetic has its advocates, especially in the U.S.A. and on the Continent. In the series of Mathisen,[25] of Oslo, it is used throughout, and in many others it is predominant.

Table VII.—Type of Anæsthesia

	General Anæsthesia	Spinal Anæsthesia (Percaine, 1–1500)
Adult males	35	100
Adult females	8	3
Children (under 17)	17	0
Total	60	103

In children and the more nervous adults, especially women, general inhalation anæsthesia is indicated, but for the average male adult spinal anæsthesia is ideal, and, as will be seen from the above table, was used extensively in this series.

Fite[11] also strongly advocated this, claiming for it that better relaxation is obtained, that there is no œdema (as may be found with local injections), and that the handling of a number of successive cases is facilitated. West, Gibson, and Cupp[37] also praise the relaxation obtained.

It is considered, also, that there is less risk of post-operative chest complications, and if the protruded mass is large, reduction is sometimes hardly possible without spinal anæsthetic. Percaine (1–1500) solution has been exclusively used, and has been found to be uniformly reliable.

Operations.—Details are given in *Table VIII*.

Operative Mortality.—In this series there was one death, a rather poorly developed man of 42 with a medium-sized primary direct right hernia (*Case* 97).

Table VIII.—TYPES OF OPERATION

	SAC ONLY	EXTERNAL OBLIQUE GRAFT	THIGH GRAFT
Children (1–16)	17	—	—
Adult females	4	1	6
Adult males	19	26	90
Total	40	27	96

A thigh graft operation was performed under spinal anæsthesia, and all proceeded normally. There was no post-operative pyrexia, but about the tenth day a " friend " with influenza on him visited him, and on the fourteenth day he was dead with influenzal bronchopneumonia.

This gives an operative mortality of 0·61 per cent, which is somewhat higher than in other comparable series: these, however, are larger and probably therefore give a more accurate picture. Gibson and Felter's[16] figure is 0·495 per cent, Erdman's[8] 0·274 per cent, and Mathisen's[25] 0·55 per cent. An analysis of the causes of death in these three series shows that of the 13 cases, 6 died of pulmonary emboli, 3 of pulmonary complications (pneumonia or bronchitis), 2 of cardiac failure, and 2 of other causes.

Complications at Operation and after Operation.—In respect of the former it is not proposed to go into great detail. There were no serious difficulties, except perhaps in the reduction of the contents of one enormous irreducible hernia containing extensively adherent large and small intestine (*Case* 71). In a number of cases other operations were performed at the same sitting, e.g., for hydrocele, varicocele, and orchidectomy, etc.

One case was of the *hernie en glissade* type, and 8 were partly or completely irreducible although not strangulated.

Post-operative complications may be tabulated briefly:—

Suppuration	3 (2 of these—*Cases* 31 and 123—later recurred. It is possible that there may have been a few cases of mild infection in addition to these)
Scrotal hæmatoma	1
Bronchitis	4 (some mild)
Small pulmonary embolism	1
Pleurisy	1 (mild)
Femoral thrombosis	1
Pneumonia	1 (the fatal case)
Whooping-cough	1

It is interesting to note that Lyle[22] found 5 cases of suppuration in 159 graft cases (3 per cent), while the corresponding figures of Mathisen[25] and Gibson and Felter[16] for mixed series (mostly non-graft operations) are 1·65 per cent and 4 per cent.

Recurrences.—*Table IX* gives the number of recurrences for all cases. There were no recurrences in children or adult females, so that the figures do not really give a true picture of the frequency of recurrence in the largest and most important class, namely, adult males. *Tables X, XI* give a clearer picture of this aspect.

Table IX.—RECURRENCES (ALL CASES)*

TYPES OF OPERATION	TOTAL HERNIÆ	UNTRACED OR TRACED LESS THAN 6 MONTHS	TOTAL TRACED HERNIÆ	RECURRENCES	PERCENTAGE
Sac only	40	1	39	4	10·2
External oblique graft	27	1	26	1	3·8
Thigh graft	96	1	95	2	2·1
Total	163	3	160	7	4·3

* Traced cases here include those that died.

Table X.—RECURRENCES (ADULT MALES ONLY)*

TYPES OF OPERATION	TOTAL HERNIÆ	UNTRACED OR TRACED FOR LESS THAN 6 MONTHS	TOTAL TRACED HERNIÆ	RECURRENCES	PERCENTAGES
Sac only	19	1	18	4	22·2
External oblique graft	26	1	25	1	4·0
Thigh graft†	90	1	89	2	2·25
Total	135	3	132	7	5·3

* Traced cases here include those that died.
† The respective figures for recurrence in indirect and direct herniæ in adult men with the thigh graft operation are 1·3 and 8·3 per cent.

Certain points can be made from these tables :—

1. Recurrence in children and adult females is rare. This appears to be true notwithstanding the fact that the simpler operations were performed in most of these cases.

2. Although, as seen in *Table IV*, the respective ages for adult male operations by 'sac only', external oblique graft, and thigh graft methods are 28·7, 41, and 44, the comparable recurrence rates are 22 per cent, 4 per cent, and 2·25 per cent. As, in addition, the thigh graft list contained all the large and more difficult, and all the direct and recurrent, herniæ, it must be agreed that this technique would appear to be far better than the others for adult men.

3. The recurrence in a number of young men after the 'sac only' and external oblique operations stresses the need for the adoption of the thigh graft method from the age of 17 or thereabouts.

4. *Cases* 57, 35, and 48, 'sac only' cases which recurred, have since been operated on by the thigh graft method—the first two by me, and the third in London—and are free from recurrence after $4\frac{1}{2}$, 4, and 4 years respectively. This again stresses the superiority of the latter operation.

The thigh graft operation series is therefore shown to have a recurrence rate of 1·3 per cent for indirect and 8·3 per cent for direct herniæ (2·25 per cent for both types) in an unselected group of adult male cases with a reasonably good follow-up, and it is claimed that these figures are better than those for other operations.

Let us compare other papers. At the risk of boredom, it must be repeated that in many cases the value of figures given is doubtful owing to the shortness and incompleteness of the follow-up, and females and children are included.

Table XI.—Analysis of Recurrences in Adult Males*

No.	Age	Time of Recurrence after Operation	Single or Double Case	Side	Size	Indirect or Direct	Primary or Recurrent	Type of Operation	Notes and Complications
		Yr. Mth.							
48	33	– 2	S	L	Complete, medium	I	Primary	Sac only	Difficulty was experienced with the anæsthetic, otherwise an external oblique graft would probably have been done
8	23	– 3	S	R	Complete, small	I	Primary	External oblique graft	No difficulty
57	19	– 5	S	R	Complete, medium	I	Primary	Sac only	No difficulty
35†	29	– 9	D	L	Complete, small	I	Primary	Sac only	No difficulty
123	55	1 2	S	L	Complete, large	D	Recurrent (twice)	Thigh graft	Suppuration, medium degree
31	65	4 6	S	R	Complete, very large, partly irreducible	I	Primary	Thigh graft	Weighed 17 st. Hernia very large: partly irreducible and of 30-year duration. Bronchitis and profuse suppuration (post-operative). Also patient insisted against advice in wearing truss after operation
34†	28	6 0	D	R	Complete, medium	I	Primary	Sac only	No difficulty

* None in children and adult females.

† Herniæ 34 and 35, same patient.

There are a large number of articles in which recurrence rates are for the Bassini operation (with or without modifications) or for a mixed series in which this type of operation greatly predominated. They are most easily understood in tabular form (*Table XII*).

Table XII.—PERCENTAGE RECURRENCE RATE AFTER BASSINI OPERATION

	INDIRECT	DIRECT	INDIRECT AND DIRECT
Block[3]	—	—	5·0
Mathisen[25]	3·18	10·0	—
Erdman[8]	3·0	16·6	7·5
Davis, L.[7]	—	15·0	7·8
West, Gibson, and Cupp[37]	4·4	—	—
Ostfeld[30]	4·3	20·0	5·4
Page[31]	20·2	25·0	—
Fallis[9]	—	—	8·25
O'Shea[29]	—	—	11·5

These will be seen to vary considerably, but a general idea of the results of this operation can be gathered.

Lyle[22] in an interesting paper showed a recurrence rate of indirect 3 per cent, direct 9 per cent, total 5 per cent, in a series of 132 external oblique graft and 27 thigh graft operations—there were actually no recurrences in the latter type—while a parallel contemporaneous series with the Bassini technique and modifications showed corresponding recurrence rates of 9 per cent, 14 per cent, and 10 per cent, and in addition he remarks that the grafted cases had definitely far larger and more difficult herniæ. Zimmerman[38] gives a 10·2 per cent recurrence for direct herniæ with a repair operation using a flap (not strip) from the external oblique.

Fleming[12] reports on 44 operations where a flap from the fascia lata is obtained through the retracted inguinal incision, and is used to strengthen the weak area in the inguinal canal. Four cases suppurated and recurrence followed in every one of these, but not in any of the other 40. He advises the use of fascial flap in all except small primary indirect herniæ in young people or children.

Finally, let us turn to the strip thigh graft series.

Watson[36] decries the fascial graft, but the figures he quotes are in many cases old.

Burdick, Gillespie, and Higginbotham[4] were disappointed with the use of fascial graft. It is difficult fully to analyse their figures, as not only were all types of herniæ included, but ox fascia and homologous strips were employed as well as the usual autogenous graft. They give the recurrence rate of 15·4 per cent in primary autogenous indirect inguinal cases. There was a very high suppuration rate with all types of graft, although least with the autogenous. Only with the more severe herniæ was graft used. In spite of all these allowances this recurrence figure must be considered as bad; but is their opinion of graft results generally held? It is certainly not, as will be seen.

Behrend[1] gives the excellent figure of 2·4 per cent for indirect and direct cases. He seconds my views, when he states that fascia should be used in nearly every primary operation except in children, and that there is no question about its efficacy in recurrent hernia. He adds that in his opinion even after infection the use of fascia reduces the danger of recurrence.

Masson[23] is also in general agreement. In children and young adults he considers the smallest operation suffices. Results in other cases without graft are so surprisingly bad that he advocates the external oblique graft for all ordinary indirect herniæ, but if the muscles are poor then the thigh graft operation should be done. He adds that by these methods not only will the percentage of cures be higher, but many herniæ previously considered inoperable can be cured, especially if a spinal anæsthetic is employed.

Swinton and Schwalm[34] are also strongly in favour of thigh grafts. In their opinion not only should all recurrent and direct herniæ be repaired with fascial grafts, but they now believe that fascial transplants should be utilized more and more in indirect herniæ in men, especially in those who will be compelled to do heavy work following operation.

Other writers such as West, Gibson, and Cupp[37] and Mathisen,[25] although not employing grafts for indirect cases, nevertheless advocate their use in direct herniæ.

Finally Fallis[10], after showing a 13 per cent recurrence with the Bassini operation, using silk, in 200 recurrent herniæ, remarks that fascia was not used at all, but in view of the large number of operative failures he is now using living sutures in all cases of poor musculature, multiple recurrence, or where tissue loss from infection has occurred.

Causes of Recurrence.—In this series the causes can be simply stated as :—

Ill-judged type of operation	5 cases
Suppuration	2 cases (1 case also had bronchitis)

Numerous other writers have enlarged on this aspect, and they are in general agreement.

Page[31] neatly summarizes the causes as : (1) Technical method used (cf. above figures) ; (2) Failures of operative technique, viz., actual wrong technique in operation chosen, suppuration, hæmatoma, etc. ; (3) Chest complications ; (4) Double operations ; and (5) Hereditary tendency to hernia or congenital feebleness of muscles.

Clearly, not only can the wrong operation be chosen, but faulty technique can also contribute to the recurrence rate. Certain important points in the thigh graft operation such as starting the ' darn ' close to the pubic spine have been stressed. Incomplete isolation of the sac is perhaps the most important factor. In addition, premature return to the erect position and to full work must not be allowed if recurrences are to be avoided.

Suppuration and hæmatoma are agreed to be important factors : Davis[7] found that they were respectively responsible for 6 per cent and 13 per cent of his recurrences ; Bessin[2] showed suppuration to have preceeded 10 per cent of his recurrences ; while both Lyle[22] and Grace and Johnson[17] state that they consider 40 per cent of cases with suppuration are followed by recurrence. West, Gibson, and Cupp[37] put the figure at 64 per cent. Suppuration is definitely more common in recurrent than primary cases (Grace and Johnson[17]), and it must be agreed with these writers and with Burdick, Gillespie, and Higginbotham[4] and O'Shea[29] that infection is rather more common with the fascial graft operation. It must, however, be remembered that in most series the grafts are reserved for the more difficult obese and recurrent patients, where there is always more risk of infection in any case.

Chest complications are responsible for a fair percentage of the recurrences. Davis[7] shows that 18 per cent and Bessin[2] 50 per cent of recurrences were secondary to these.

The performance of the bilateral operation at the same sitting is reported to be another predisposing factor. Gallie and Lemesurier[15] found recurrence more common in these cases, and suggested that it was due to the technique being more hurried and so less efficient. Fallis[9] also finds recurrences more common in double operations. In the author's series there was 1 double recurrence, but it is difficult to draw any definite conclusion for or against the above opinion from this.

Obesity, which makes operation more difficult, certainly makes recurrences more possible. Fallis[9] has shown that recurrence is 50 per cent more common in fat patients than in the average for the whole of his series.

The Time of Recurrence.—Table XIII strongly re-emphasizes the point that has been made before, that the longer the follow-up is continued the larger the number of recurrences, and that follow-ups for but 6, 12, or even 24 months give a wholly erroneous view of the recurrence rate, for as will be seen from the table, 2 cases (28 per cent of the total) recurred after 2 years, the actual times being $4\frac{1}{2}$ and 6 years respectively.

Table XIII.—Time of Recurrence

Time of Recurrence	No. of Hernia	Percentage of Recurrence (Each Category)	Percentage of Recurrence (Cumulative)
Under 3 months	2	28·55	28·5
4–6 months	1	14·3	42·8
7–12 months	1	14·3	57·1
13–24 months	1	14·3	71·4
Over 2 years	2	28·55	100·0
Total	7	100·0	—

One cannot agree with Behrend[1] when he states that most recurrences take place almost immediately after operation, or with Davis,[7] who suggests that most are seen within 6 months. Fallis,[9] with 50 per cent under 1 year and 67 per cent under 2 years, is in close accord with the above table, and so to a lesser extent is Mathisen[25] with 50 per cent under 6 months, 80–90 per cent under 1 year, and 93 per cent under 2 years. If the latter's follow-up had been longer than 3 years in most cases, it is thought that his figures would have been approximated more closely to the author's.

It is held, then, that while a large number of herniæ recur soon, some 40 per cent in under 6 months and 70 per cent before 2 years have passed, an appreciable proportion, nearly 30 per cent in this series, may be expected even after this time has elapsed.

After-effects.—A special point has been made in the course of the follow-up of questioning the patients as to pain in the groin or thigh (in the case of thigh grafts) and as to efficiency to do their work after operation.

Table XIV shows that a certain number of thigh graft cases had occasional slight pain, ache, cramp, stitch, smarting, or discomfort in the thigh, and in

addition a few others had irritation or an occasional feeling of weakness. There was no case of severe or continuous pain. It should be noted that these troubles, minor as they are, are far less common in proportion to numbers of cases with the newer subcutaneous method of obtaining the graft by fasciotome than in the open operation with the longer thigh scar.

Table XIV.—Discomfort after Operation

Operation	Total Number of Herniæ	Groin		Thigh		
		Occasional Ache, Smart, Cramp, or Stitch	Occasional Irritation	Occasional Ache, Smart, Cramp, or Stitch	Feeling of Slight Weakness	Occasional Irritation
Sac only	40	5	–	–	–	–
External oblique graft	27	2	1	–	–	–
Thigh graft:						
Open incision	19	5	–	4	1	1
Fasciotome	77	14	–	5	2	1
Total	96	19	–	9	3	2
Grand Total	163	26	1	9	3	2

The more important point, however, is that no fewer than 19 thigh graft patients, or 27 of all classes of operation, had some slight discomfort of one type or other in the groin.

Many writers who condemn thigh grafts on account of subsequent weakness or pain in thigh, do not mention whether they have inquired also into the question of groin pain, but Davis[7] found 50 out of 754 cases have pain or other groin discomfort 1 year after operation. Erdman[8] and West, Gibson, and Cupp[37] also quote figures, but do not state the nature of the follow-up. Care was taken at operations to avoid injury to the nerves, and it is not thought that pain was due to nerve involvement, but rather to the mild pain that follows a proportion of all scars. Several patients say they notice it in wet weather particularly.

It must also be remembered that in many cases the discomfort, slight even as it may be, passes off entirely after a few months or even later, and so a number of the cases recorded above, especially the more recent, may be expected to be excluded later.

It might well be thought that the gap left in the fascia lata in the fasciotome operation might often cause weakness. A hernia of the underlying muscle is seen to a varying degree, usually slight, in a number of cases, but without symptoms in most cases.

One entirely agrees with Masson,[23] who states that hernia of muscle which occurs in some cases is of no importance, and patients should be strongly advised not to have an operation for its repair.

As to efficiency after the thigh graft operation (and in fact the other operations) none of the patients who were working before operation have been unable to return to their usual work after operation, while a few previously for some time unfit for heavy work have been so improved as to be fit for full hard manual labour.

A number of cases follow very strenuous occupations such as wielding a heavy hammer, furniture moving, stoking, etc., while others indulge in vigorous sports—several play for football teams of some merit, one man has cycled 400 miles a week on holiday, while a man of over 60 with a 22-year-old history of hernia now walks 12 miles a day without discomfort.

DISCUSSION

Surgeons, as has been said earlier, wish to know, from experience gained from proved results, what is the most effective operation for a given condition.

There is no doubt from all statistics that in the herniæ of children the simplest of operations suffices. The 'sac only' operation is therefore by general agreement fully adequate and no other need be considered in these cases.

Statistics in the category of adult women (as apart from men) are for the most part lacking, but the consensus of opinion is that whatever the operation may have been, recurrence in females is rarer than in males, and this view is supported by the absence of any female recurrence in my own series. In this series the larger female herniæ were subjected to a graft operation.

The question then is whether or no a 'sac only', or perhaps for the larger sacs an external oblique graft, operation is sufficient, or whether adult females also in spite of the apparent infrequency of recurrence should be subjected, as this paper aims to show is desirable for men, to a thigh graft operation.

I consider that most adult female herniæ should have a thigh graft operation performed, but perhaps rather more latitude may reasonably be allowed. The performance of the smaller operation is probably justifiable in young women with small sacs, but at present I do not propose as a general rule to adopt this in continuing the present series.

The real question of course is the choice of operation in adult men, and it is clear from the preceding sections that opinion here is divided.

The pros and cons of the thigh graft operation must be discussed. Take the reputed drawbacks first: It does definitely take longer than the 'sac only' or Bassini operations, but the fasciotome and fascial introducer have shortened this by avoiding the lengthy labour of sewing up the thigh and the time spent in threading and suturing the fascial strip to a Gallie needle, and with but little practice the average time can be brought down to 35 or 40 minutes, while in favourable circumstances 27 minutes have sufficed.

Discomfort or pain in the thigh does in a certain number of cases follow the thigh graft operation, but, as has been shown, with the fasciotome this is less frequent than with the open operation, and in any case is not a serious objection. It has not stopped any man from restarting his job.

Infection has in some papers been shown to be more common with the thigh graft operation than with the other types, but it is felt that this finding is due mostly to the fact that the majority of surgeons have so far reserved the graft technique for the recurrent, stout, large, or difficult cases—in this series both cases of suppuration after graft were in this category—and that it is often really the nature of the hernia rather than the fascia that is culpable.

It is claimed that the statistics of this series, and comparison with other figures, prove that for the adult man the Gallie operation gives appreciably better results than any other.

If then the results are better, surely it is worth the extra time, for it is a well-known fact that the first operation on a hernia is far the easiest, and it is surely better in all men over 17 to take rather longer in the first instance and use a graft than have to operate again and perform a difficult recurrent operation in an older patient with no choice but a graft and less hope of cure.

Such, then, it is thought, is the opinion to be drawn from these investigations, and it is felt that the adequate follow-up on similar lines of series of the thigh graft and Bassini or other operations for hernia will prove these facts conclusively, and the increased use of fascia will bring the results of hernial surgery to a far higher level.

SUMMARY

1. A personal consecutive series of 163 elective operations for inguinal hernia is reported.

2. The literature is reviewed with special reference to (*a*) recurrence with fascial graft operations as compared with other methods, and (*b*) follow-up of hernial operation cases.

3. The inadequacy of the average existing follow-up is stressed and the ideal is delineated.

4. The various facets of recurrence are discussed.

5. Recurrence rates of 1·3 per cent in indirect and 8·3 per cent in direct herniæ in adult men with the thigh fascial graft technique are shown.

6. The advantages and disadvantages of this operation are discussed.

7. While it is thought that for herniæ in children up to 16 the 'sac only' operation is sufficient, it is strongly advocated that all other non-strangulated inguinal herniæ should be submitted to the thigh graft operation.

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A BRONCHOSCOPIC CLINIC

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THE recent publication of two papers which were read at the Summer Meeting of the British Medical Association by Negus (1939) and by Martin (1939), has encouraged us to describe briefly the work and methods used in a Bronchoscopic Clinic which we inaugurated over six years ago with the help of our colleagues.

Although peroral endoscopy includes direct inspection of the hypopharynx, larynx, trachea, bronchi, œsophagus, and stomach, in this Clinic we have devoted most of our interest to *bronchoscopy*. Œsophagoscopy also has been carried out, but gastroscopy has not been attempted owing to the want of a flexible gastroscope.

The Clinic is held once weekly and it is our experience that the optimum and maximum number of patients that can be examined at a session is four. Altogether up to the outbreak of war we had performed 937 bronchoscopic examinations on 581 patients—442 males and 139 females. Not unexpectedly in a number of these, the findings were negative in regard to any visible bronchial lesion. Of our series of 581 patients no abnormality was detected in 130 (22·4 per cent) by the bronchoscope.

We consider that a feature of great importance has been the compilation of full notes of the cases, a careful follow-up of all patients, and, whenever possible, the performance of autopsy on those who died.

PERSONNEL

Bronchoscopy in trained hands is a safe and harmless procedure even in the presence of serious pulmonary disease. It is not a 'one-man' operation, but its successful conduct and the interpretation of its findings are dependent upon team work. A team must have as its minimum a physician, a radiologist, a laryngologist, a thoracic surgeon, and trained assistants.

We have been fortunate to have the valuable radiological help of Dr. J. H. Mather and his staff, and the generous surgical advice of Mr. J. T. Morrison.

ANÆSTHESIA

For *adults* our method of anæsthesia for bronchoscopy is to give phenobarbitone, gr. 1, by mouth the night before operation, and a similar dose of the drug on the morning and at lunch-time of the day of operation. Morphia, gr. $\frac{1}{4}$, and atropine, gr. $\frac{1}{100}$, are given $1\frac{1}{2}$ hours before operation. A quarter of an hour before passing the bronchoscope the roomier nasal fossa, the pharynx, and glottis are sprayed from a de Vilbiss atomizer with a solution containing $2\frac{1}{2}$ per cent cocaine

and 25 per cent of 1–1000 liq. adrenalini. A gum-elastic catheter is then inserted via the anæsthetized nasal fossa through the glottis and 1–2 c.c. of the cocaine-adrenaline solution is injected into the trachea; a widespread anæsthesia of the tracheo-bronchial tree is achieved by positioning the patient after injection of the solution. The tongue, lips, and alveoli are swabbed with a mixture of equal parts of 10 per cent cocaine solution and 1–1000 liq. adrenaline.

For *children* atropine, gr. $\frac{1}{100}$ hypodermically, is the only premedication employed and a full dose of avertin is given per rectum. As a rule, however, it is necessary to supplement this with light chloroform inhalation anæsthesia.

For *œsophagoscopy* we use chloroform anæsthesia for both adults and children.

INSTRUMENTS

The bronchoscopes we have used latterly are those designed by one of us (McGibbon, 1937) with distal and lateral lighting, and we have found that these afford an excellent view except through the infant sizes, in which the lateral lights cause too much glare.

The œsophagoscopes we employ for inspection and for removal of foreign bodies are of the pattern designed by John Roberts of Liverpool. For dilatation, intubation, and insertion of radon seeds we use Souttar's (1927) œsophagoscopes.

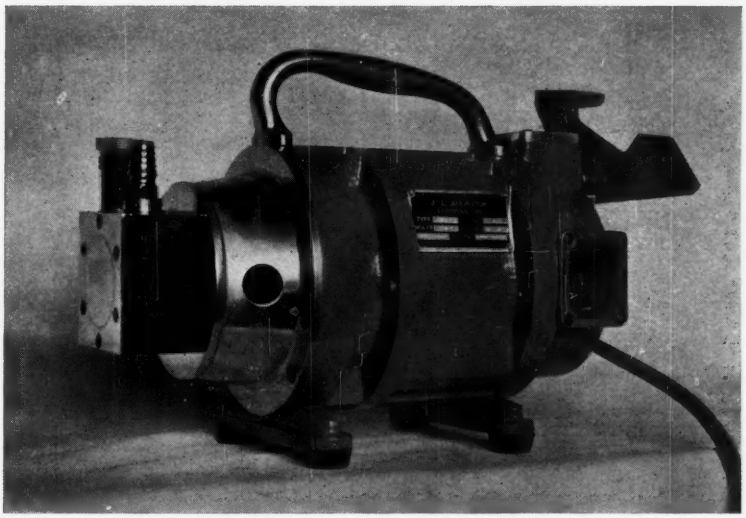

FIG. 241.—Portable universal motor suction apparatus, as described in text.

Many types of bronchoscopic forceps are obtainable, but we now use a design of our own, which have a universal handle, interchangeable tips, and the proximal end of the shaft is curved so that the operator's hand is not in the line of vision when in use. Not infrequently we use the more robust œsophageal forceps for the purpose of obtaining specimens of bronchial new growths.

After an adequate trial of Haslinger's head-rest we are of the opinion that the best co-operation from a patient during bronchoscopy under local anæsthesia can be obtained when the head is held and its posture manipulated by an assistant.

For œsophagoscopy the head is not held, but the scapular region of the patient is raised when the lower third of the œsophagus is to be examined. For this purpose we have had an operating table constructed with a 'bridge' 12 in. from its proximal end which can be elevated as required.

Efficient suction is very important during endoscopy, and we use the suction apparatus designed by Mollison (1933). If we are obliged to work outside hospital we use a small portable universal suction apparatus designed and made by J. L. Mayhook with the advice of Mr. M. Bennett-Jones (*Fig.* 241).

BRONCHOSCOPIC PROCEDURES

In the majority of cases of disease of the lung a correct diagnosis can be made from a consideration of the history, clinical findings, examination of the sputum, and investigation of the tracheobronchial tree by direct and contrast radiography. If, however, in spite of these measures the nature of the lesion has remained in doubt, direct inspection of the trachea and bronchi has been of invaluable assistance. It is not suggested that the entire bronchial tree is accessible to visual inspection through the bronchoscope, but as a rule the trachea, main bronchi, and a variable extent of the segmental bronchi can be examined directly.

Some patients have been referred to the Clinic for specified purposes only, such as the following :—

1. *Removal of Uncontaminated Specimens of Secretions and Pus.*—This has been done by suction or by swabbing. Such specimens have been required in order to ascertain the nature of the organisms present in the bronchi—particularly is this of value in persistently sputum-negative cases of suspected tuberculosis—or they have been required for the preparation of vaccines.

2. *Instillation of Lipiodol or Other Radio-opaque Oil.*—It has been our experience that for bronchography in *children* the best results have been obtained by the instillation of radio-opaque oil through a bronchoscope after avertin anæsthesia.

For *selective* bronchography of a bronchopulmonary segment or of a lobe in *adults*, in our hands the bronchoscopic route has been the most accurate method.

3. *Removal of Pieces of Tumour for Histological Examination.*—This has been attempted in all cases of bronchial tumour, but as the specimens were usually very small it has been sometimes difficult for the pathologist to express a definite opinion. Of our total series of 581 patients, 263 were considered to be suffering from bronchial carcinoma. Positive biopsy was reported, however, in only 130 of these cases—i.e., in about 50 per cent. This proportion of positive biopsies corresponds very closely with those of a series of cases reported by Ormerod (1933).

BRONCHOSCOPIC FINDINGS

The main symptoms and signs for which patients have been referred for bronchoscopic examination are relatively few, but the findings have been more numerous, diverse, and often surprising. *Table I* shows in the first column the common symptoms and signs for attendance at the Clinic, and the second column shows the frequent bronchoscopic findings.

It can be understood readily how a simple or malignant new growth, a mass of granulation tissue surrounding a foreign body or lining a bronchus leading to an abscess cavity, granulations caused by tuberculosis or syphilis, ulceration over

a calcified gland, or a tumour pushing through the wall into the lumen of a bronchus, may give rise to recurrent hæmoptysis.

Table I.—Reasons for Bronchoscopy, with Examination Findings

Presenting Symptoms and Signs	*Bronchoscopic Findings*
A. Hæmoptysis—recurrent and unexplained	1. Non-radio-opaque foreign body 2. Blood-clot 3. Inspissated bronchial secretion 4. Simple suppuration 5. Parasitic infections 6. Granuloma :— *a.* Non-specific *b.* Specific : i. Tuberculosis ii. Syphilis 7. Pressure from without the bronchus :— *a.* Calcified lymphatic glands *b.* Tumours 8. Neoplasms :— *a.* Simple *b.* Malignant
B. Dyspnœa—unexplained, paroxysmal, or continuous	
C. Pulmonary collapse — segmental, lobar, or massive	
D. Pulmonary suppuration — bronchiectasis, lung abscess, gangrene, or empyema	
E. Pneumonitis and so-called unresolved pneumonia	
F. Suspected bronchial neoplasm	

The explanation of the relationship between the remaining bronchoscopic findings and the presenting symptoms and signs is largely a mechanical one and is the result of complete or incomplete bronchial obstruction. The lesions produced by bronchial obstruction depend upon its degree—partial or complete—the rapidity of its occurrence, the size of the bronchus occluded, the nature of the obstructing agent, its mobility, and the virulence of the organisms present.

Incomplete Bronchial Obstruction leads to the retention of secretions distal to the obstruction and ' drowned ' lung, giving rise to the clinical findings of ' pneumonitis ', ' unresolved pneumonia ', or pulmonary suppuration, or it may act as a check valve and cause varying clinical pictures depending on the factors mentioned above. The earliest manifestations of bronchial obstruction may be those of an obstructive emphysema. This condition is produced by a ball-valve action of the obstructing agent whereby air can pass into the bronchi distal to the obstruction, but on expiration the ball-valve closes and air cannot be expelled. This early condition is not commonly seen except by radiologists, but it gives rise to a typical clinical syndrome recently described fully by Maxwell (1940). There is frequently an expiratory wheeze audible at the mouth, in marked cases the affected lobe or lobes are hyper-resonant, the trachea and mediastinum are displaced *away* from the affected lung, the diaphragm on that side is displaced downwards, and the intercostal spaces are widened.

Complete Bronchial Obstruction may be brought about by many different agents, and when this occurs the air distal to the occlusion is rapidly absorbed—in experimentally produced complete bronchial obstruction this takes place in only a few hours—and the affected segment, lobe, or entire lung becomes airless, resulting in ' *absorption* ' *collapse.*

The main clinical features of collapse are dullness and absence of breath sounds over the affected area, with retraction of the trachea, heart, and mediastinum *towards* that side. Pulmonary collapse due to bronchial obstruction leads rapidly to pneumonitis and pulmonary suppuration, which may take the form of bronchiectasis, abscess (single or multiple), or gangrene.

It is from the sequential symptoms and signs of bronchial obstruction only that a diagnosis frequently, but erroneously, is made, as these may completely overshadow the primary cause unless this is suspected and sought for.

SIGNS AND SYMPTOMS REFERRED TO BRONCHOSCOPY

The signs and symptoms for which patients have been referred to the Clinic are discussed briefly below :—

A. **Hæmoptysis** was the most common symptom for which patients were sent for bronchoscopic investigation. In our series of 581 patients 222 suffered from some degree of hæmoptysis—in many of them it was the predominant symptom—and the findings by bronchoscopic examination of these cases is shown in column *A* of *Table II.*

It frequently had been assumed in the first instance that the causative lesion of the hæmoptysis was pulmonary tuberculosis because of the widespread incidence of this disease, and sometimes these patients had been referred to sanatoria. Such an assumptive diagnosis should never be accepted as final in the presence of persistently negative sputum no matter how suggestive are the clinical and radiological features. There were 21 patients suffering from recurrent hæmoptysis referred to the Clinic from sanatoria, and the findings in these cases are shown in column *B* of *Table II.*

The occurrence of hæmoptysis in cases of cardiac disease does not necessarily indicate that the bleeding is due to secondary pulmonary congestion. We have examined a man aged 36 years suffering from mitral stenosis with hæmoptysis due to carcinoma of the bronchus which gave rise to no physical or radiological signs. This patient previously had been admitted to a sanatorium and he died later from a profuse hæmoptysis.

There is also a group of patients who suffer from recurrent hæmoptysis and who exhibit no physical or radiological signs of pulmonary disease. In a number of these we have found non-obstructive lesions of the bronchi (McGibbon and Bates, 1937), and the causative lesions in 15 such cases are shown in column *C* of *Table II.*

Table II.—Analysis of Bronchoscopic Findings in 222 Cases of Hæmoptysis

A. Total Cases of Hæmoptysis		*B.* Cases of Hæmoptysis Referred from Sanatoria	*C.* Cases of Hæmoptysis without Clinical or Radiological Signs of Pulmonary Lesion
Negative	54	–	–
Non-radio-opaque foreign body	2	1	1
Suppuration	23	4	–
Broncholith	1	–	1
Non-specific granuloma	1	–	1
Syphilis	1	1	1
Hydatid cyst	1	1	–
Simple new growth	13	1	4
Malignant new growth	119	13	5
Extrabronchial pressure	7	–	2
Total	222	21 (9·4 per cent)	15 (6·7 per cent)

Fig. 242 illustrates a fibroma of the left lower bronchus which gave rise to no physical or radiological signs in a man aged 27 years who suffered from recurrent hæmoptysis.

It is interesting to note that in our series of cases hæmoptysis was a symptom in 100 per cent of patients suffering from simple new growth, whereas it occurred in 45·2 per cent only of cases of malignant neoplasm.

B. **Dyspnoea** associated with attacks of coughing and wheezing may occur in cases of bronchial obstruction from any cause. In our series dyspnœa has been a frequent complaint of patients suffering from bronchial carcinoma, and this symptom was usually very marked when the trachea was involved by neoplasm or by pressure from without. Four patients only were referred to the Clinic on account of dyspnœa, and our findings were negative in one case, extratracheal pressure in another, and in two malignant bronchial new growth.

FIG. 242.—Fibroma of left lower bronchus of a man aged 27 years who suffered from recurrent hæmoptysis. On two occasions the patient exhibited signs of collapse of his left lower lobe due to bronchial obstruction by blood-clot.

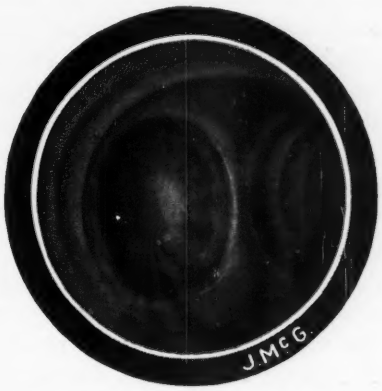

FIG. 243.—Non-ulcerated carcinoma occluding the left main bronchus of a man aged 47 years, which gave rise to 'massive' collapse of the left lung. This tumour shrank to half its size after treatment by deep X-ray therapy.

C. **Pulmonary Collapse** may be segmental, lobar, or massive, and it is commonly an absorption collapse due to bronchial obstruction. The cause of pulmonary collapse is almost always speculative until bronchoscopic examination has been carried out. Our common findings in *children* have been inspissated secretion and non-radio-opaque foreign bodies; in *adults* carcinoma has been most frequently encountered, but we have found also foreign body, blood-clot, granuloma, simple new-growth, and pressure from without the bronchus.

Fig. 243 shows the bronchoscopic findings in a case of massive collapse of the left lung due to complete occlusion of the left main bronchus by a non-ulcerated carcinoma in a man aged 47 years.

Interesting, and often unrecognized, causes of collapse are inspissated secretion and blood-clot. Bronchial obstruction by mucus plugs is now recognized as the cause of *post-operative pulmonary collapse*, which may supervene very shortly after operation, and which may vary from a segmental distribution to massive collapse of the entire lung depending upon the size of the obstructed bronchus. Until recently this condition was called 'post-operative pneumonia', but true pneumonia rarely occurs before the end of the first week after operation.

Bronchial obstruction caused by inspissated secretion may also give rise to signs and symptoms simulating unresolved pneumonia. We recently published an account of this finding in 18 children who were considered to be suffering from unresolved pneumonia.

Blood-clot derived from a local lesion in the lung or from aspiration may act as an obstructing agent. The fibroma illustrated in *Fig.* 243 gave rise to recurrent hæmoptysis and on two occasions the patient suffered from absorption collapse of his left lower lobe owing to bronchial obstruction by blood-clot; we have seen collapse produced in a similar manner in patients suffering from bronchial angioma, hydatid cyst, and foreign body.

D. **Pulmonary Suppuration** in its broadest sense—including suppurative pneumonitis, lung abscess, bronchiectasis, and empyema—should be regarded not as a disease *sui generis*, but rather as the end-result of a variety of conditions, a common cause being bronchial obstruction, partial or complete, from one of the causes mentioned above.

Bronchoscopy, therefore, is of the greatest value—indeed it is an essential investigation—in every case of suppurative disease of the lung, as the character and source of the pus, the exact nature of the causative lesion and the degree of obstruction to drainage cannot be ascertained until direct inspection of the bronchi has been made. Of our series of 581 patients there were 90 whom we considered to be suffering from simple pulmonary suppuration—abscess and bronchiectasis—and 1 from gangrene: in 8 of these the suppurative condition was secondary to impacted foreign bodies.

Fig. 244 shows a non-radio-opaque foreign body (mutton-bone) discovered by bronchoscopy in a patient aged 57 years, suffering from pulmonary suppuration, who two years previously had been diagnosed as suffering from bronchial carcinoma.

E. **Pneumonitis and Unresolved Pneumonia.**—Pneumonitis is a recently introduced term used to define a non-specific reaction of the lung parenchyma to a variety of causes. It may resolve or proceed to frank suppuration. The bronchoscopic findings in our series of cases have been those of partial or complete bronchial occlusion.

FIG. 244.—Foreign body (mutton bone) impacted in left lower bronchus and surrounded by granulations in a man aged 57 years. He suffered from the effects of pulmonary suppuration, and two years previously he had been diagnosed as having bronchial carcinoma.

FIG. 245.—Inflammatory swelling of ostium of right posterior basal bronchus of a child aged 7 years, who was considered to be suffering from unresolved pneumonia.

In a recent series of 38 patients (McGibbon, Bates, and Mather, 1939) incorrectly diagnosed as suffering from unresolved pneumonia, we found the real cause to be one of the following: inspissated secretion, impacted foreign body, simple pulmonary suppuration, bronchial neoplasm, or extrabronchial tumour.

Fig. 245 shows inflammatory occlusion of a right basal bronchus of a child aged 7 years who was considered to be suffering from unresolved pneumonia.

F. **Pulmonary Neoplasms.**—*Simple new growths* of all varieties have been described in the tracheobronchial tree, as elsewhere in the body. We have encountered only 13 cases of simple new growth—10 angiomata, 2 adenomata, and 1 fibroma—and the common symptoms in our cases were cough, recurrent hæmoptysis, and those caused by bronchial obstruction, partial or complete

The only cases of simple new growth recognized during life have been diagnosed by the bronchoscope, and many of these neoplasms are curable by endoscopic methods if they are seen early.

Fig. 242, described above, shows the bronchoscopic appearances of a fibroma of the left lower bronchus.

Malignant new growths may be either primarily tracheal or bronchial in origin, or they may be secondary to direct spread from neighbouring structures or to metastases from distant foci.

We have examined 263 patients—230 males (52 per cent of total males examined) and 33 females (23·7 per cent of total females examined)—in whom our bronchoscopic findings were consistent with carcinoma, although positive biopsies were reported in only 130. The records of the positive biopsies are shown in *Table III.*

Table III.—Histological Reports of 130 Cases of Bronchial Carcinoma

'Malignant'	11
'Carcinoma'	69
Oat-celled carcinoma	20
Anaplastic carcinoma	3
Epithelioma	3
Columnar-celled carcinoma	12
Squamous-celled carcinoma	12

From the point of view of diagnosis we attach more importance to the bronchoscopic view than to the reports on sections of tissue removed, as the pathologist is handicapped by the small size of the specimens and by the secondary inflammatory changes which always take place on their surface, and we are of the opinion that bronchoscopy affords the most reliable means of arriving at a positive diagnosis of *early* bronchial carcinoma. This is a matter of urgency if full advantage is to be gained by the rapid advances that have been made in thoracic surgery.

It is generally recognized that the early symptom of bronchial carcinoma is cough, often accompanied by hæmoptysis. We have seen several patients in whom these symptoms have been present, who have exhibited no clinical or radiological signs of pulmonary disease, and in whom the instillation of lipiodol failed to reveal any abnormality. These patients were often young, they felt and appeared to be in good health, but bronchoscopy demonstrated unequivocal evidence of early malignant disease.

Such early growths often show merely fixity of the bronchial wall or distortion of its rings (*Fig.* 247), or there may be a tumour or ulceration which does not completely obstruct the lumen.

In the moderately advanced stage the *presumptive* diagnosis of malignancy usually presents no difficulty, but the existence of carcinoma cannot be *proved* unless malignant cells or small masses of tumour are demonstrated in the sputum, until the disease has advanced to such a degree that secondary glands are available for section, or metastatic deposits have occurred elsewhere. In our series, in spite of routine examination of all patients' sputum, only in a few advanced cases of malignant bronchial neoplasm have we received positive reports as to the presence of malignant cells or tumour masses. In this stage of the disease bronchoscopic examination has revealed lesions which are characteristic—fungating granulations

FIG. 246.—Fungating carcinoma of right main bronchus of a man aged 49 years.

FIG. 247.—Early carcinoma of lower end of trachea, showing distortion and fixation of the tracheal rings, in a man aged 57 years.

(Figs. 242–247 are the authors' original drawings, here reproduced by kind permission of the Editor of the 'Sphincter'.)

surrounding and occluding the bronchial lumen, which bled readily from the slightest trauma and were situated on an obviously infiltrated base (*Fig.* 246), or less frequently we have seen what appeared to be a smooth non-ulcerated red tumour partially or completely occluding the bronchus (*Fig.* 243).

In our series of cases the neoplasms were present with almost equal frequency in either the right or left bronchial tree; there were 4 patients in whom new growths were visible in both main bronchi, apparently as a result of implantation, and one man aged 35 years died from carcinoma of his right middle-lobe bronchus which we assumed to be an implant from a new growth of his palate and tonsil, which had been treated with radium five months previously.

In some cases it was impossible by inspection alone to make a differential diagnosis between simple and malignant new growths. Frequent observation and repeated biopsy were necessary before the true nature of the growth was determined. Pulmonary syphilis also is indistinguishable from carcinoma by the bronchoscope. Biopsy does not necessarily settle the diagnosis, nor does a positive Wassermann exclude malignancy, as the two conditions may coexist. We have seen 3 cases (1 female and 2 males) in which we diagnosed a specific lesion of the bronchus: one patient (female) cleared up completely with antiluetic treatment, one was greatly improved, and the third one is untraced.

BRONCHOSCOPIC THERAPY

Therapeutic measures that we have employed through the bronchoscope consist of the following :—

1. Removal of foreign bodies.
2. Drainage of suppurative lesions by suction.
3. Lavage of bronchiectatic and abscess cavities.
4. Installation of antiseptics.
5. Dilatation of inflammatory strictures.
6. Removal of granulations and of simple and malignant neoplasms.
7. Diathermic coagulation of simple and malignant neoplasms.
8. Insertion of Tudor Edwards's tube with radon seeds.
9. Interstitial insertion of radon seeds.

In our experience suppurative lesions which can be drained by suction are treated quite as adequately by efficient continuous postural drainage carried out on a special bed of the Nelson type ; but we would emphasize the necessity of at least one initial bronchoscopy in order to determine the nature and site of the causative lesion.

We have occasionally observed improvement following bronchoscopic instillation of antiseptics into, or lavage of, abscess cavities ; but our results have never been so gratifying as those reported by some other observers.

The remaining bronchoscopic therapeutic measures have been aimed at establishing and maintaining patency of the bronchi, as it is recognized that a blocked bronchus from *any* cause soon leads to permanent pulmonary suppuration. The measures we have adopted have been removal of exuberant granulations and of simple and malignant new growths by biting forceps, and destruction of similar lesions by diathermy or by the interstitial insertion or intralumenary application of radon seeds.

We have treated 124 patients with radon seeds. Unfortunately the present conditions have interrupted the follow-up of these cases, so that it is impossible to quote comprehensive figures in regard to results, but we are convinced that such treatment is of very great value in the alleviation of symptoms. The majority of these patients also received a course of deep X-ray therapy, and in spite of other expressed opinion we consider this latter form of treatment to be of great value. We watched the intrabronchial tumour illustrated in *Fig.* 243 shrink to half its size, with complete relief of bronchial obstruction, for some months before death, following deep X-ray therapy alone.

The importance of re-establishing adequate bronchial drainage in this type of case is not generally appreciated. We have seen numerous patients with advanced malignant disease of the bronchus whose symptoms have been largely due to the sequential suppuration. Once bronchial drainage has been afforded, marked improvement has taken place, and in several instances patients have been enabled to resume work up to periods of 2½ years—not only has life been prolonged, but suffering in some cases has been considerably reduced.

In conclusion we agree with the two speakers mentioned at the outset of these notes in regard to the necessity for the establishment of Endoscopic Clinics. We consider, however, that such Clinics should not be too numerous, otherwise this speciality would become so decentralized that the cases would of necessity be

relatively few, and the knowledge to be gained by a large experience would not be available and the quality of the work as a result would suffer. Finally the question whether endoscopy " should remain under the speciality of laryngology or become a branch of thoracic surgery " should not arise—it should be the work of a team which should include both laryngologist and thoracic surgeon, as suggested earlier in these notes.

Our thanks are due to our colleagues at the Southern Branch of the Royal United Liverpool Hospital, and to the Medical Officers of several other hospitals who have referred patients to the Clinic. Particularly are our thanks due for the radiological help of Drs. J. H. Mather, R. E. Roberts, A. P. Whitaker, and A. E. Connolly.

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SECONDARY INFECTION IN TUBERCULOUS SINUSES

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Abscess and sinus formation are the two great local complications in cases of non-pulmonary tuberculosis. Abscesses are regarded seriously and treated carefully because they may lead to sinus formation and ultimately expose the patient to the risk of mixed infection which is generally accepted as a most serious complication. Experience of such cases raised many queries which a search of the literature failed to answer, with the result that an investigation was planned to answer the following questions: (1) The nature of the secondary infecting organisms in tuberculous sinuses; (2) The time of onset and mode of ingress to the sinuses of such secondary infecting organisms; (3) The clinical effect of such a complication.

The complete investigation dealt with 132 patients of both sexes. These patients ranged from 1 to 17 years of age and were all suffering from non-pulmonary tuberculosis. That no doubt should exist regarding the tuberculous nature of the primary lesion, bacteriological proof was obtained wherever possible. Tubercle bacilli were cultured from 81 patients, and in the remaining 51, in which the specific organism was not recovered, the clinical and radiological data were considered adequate. All doubtful cases were excluded. In each case abscesses or sinuses were present and an attempt was made to make the series a representative one. The age and sex distribution of the patients are shown in *Table I.*

Table I.—Age and Sex Incidence

Age Group	*Males*	*Females*
0–5 years	14	19
5–10 years	34	26
10–15 years	17	17
15 years and over	1	4
Total	66	66

Observations on the nature of the secondary infecting organisms in tuberculous sinuses were made on 102 patients of the above series, in each of whom sinus formation was present as a complication. The number of sinuses examined was

Table II.—Site of Primary Focus and Number of Sinuses

Site of Primary Focus	*No. of Sinuses*	*No. of Cases*
Vertebræ	25	23
Hip-joint	19	18
Knee-joint	8	7
Ankle-joint	9	8
Long bones	13	12
Dactylitis	13	11
Gland and soft tissue	14	14
Miscellaneous	9	9
Total	110	102

110, some patients having multiple sinuses from a single focus, others having multiple foci each with a single sinus. The site of the primary focus and the number of sinuses arising from each area which were examined is shown in *Table II*.

1. THE NATURE OF THE SECONDARY INFECTING ORGANISMS

The routine of examination was as follows: When a dressing was removed from a sinus the skin surrounds and the superficial part of its tract were cleaned. Pus was then expressed from its depths and a loopful taken and transferred to two tubes of nutrient broth. Where the discharge was slight a platinum loop was inserted into the depths of the sinus and the exudate obtained inoculated as before. One of the inoculated tubes was then incubated under aerobic conditions and the other under anaerobic conditions. These steps were continued in subculture until it was certain that no true anaerobic organisms were present. Pure cultures of the organisms recovered were then isolated and typed in the most suitable manner. These examinations were conducted at varying periods in the course of the sinus—some at its onset, some when it was in the process of healing, some midway in its course—most of the sinuses within the series being examined on numerous occasions. Specimens of the pus obtained were also examined microscopically.

A secondary infection was present in 90 per cent of the sinuses examined, the site of the sinus making little or no difference as regards percentage gross infection. The organisms recovered were streptococci 116 strains, staphylococci 86 strains, diphtheroid bacilli 21 strains, coliform bacilli 6 strains, unidentified organisms 5 strains. No strictly anaerobic organisms were recovered.

The streptococci recovered were examined from the aspects of their hæmolytic and serological properties. Hæmolysin production was determined by culture in blood-agar plates in every instance and approximately half of the β-hæmolytic strains recovered were examined serologically by comparison with type cultures from the Lister Institute, using agglutination, absorption of agglutinin, and complement-fixation tests. Of the 116 strains 93 were β-hæmolytic in type, 18 had no hæmolytic power, and 5 had a hæmolytic power uncertain in degree. Serological tests on the β-hæmolytic strains clearly related only one to *Strep. pyogenes* and one other to *Strep. erysipelatosus* of the type cultures. Absolute identity such as this was not obtained with the others, although the tests showed that a close relationship existed between them, not only to each other but to the type cultures of the *Strep. hæmolyticus* group. Twenty of these strains were then selected at random and their virulence tested on mice. Only one of them caused death in the inoculated animals. From the morphological aspect it is interesting to note that 'smooth' colony forms were common, only three 'rough' variants being noted throughout the series and that it was one of these 'variants' which proved virulent. This lack of virulence was thought to be responsible for the lack of type specific characters in the strains examined serologically. It was concluded that the sinuses were infected with potentially pathogenic streptococci, but that their pathogenicity was low.

The 86 strains of staphylococci recovered were classified as follows: *Staph. aureus* 20 strains, *Staph. albus* 65 strains, *Staph. citreus* 1 strain. Virulence tests were conducted with 3 *aureus* strains and 5 *albus* strains. These proved the

organisms to be avirulent. Acknowledging the general opinion that *Staph. aureus* is the most pathogenic, *Staph. albus* a feeble pathogen, and *Staph. citreus* a non-pathogenic saprophyte, and adding to it the results of the virulence tests, it was felt that the sinuses were infected with potentially pathogenic staphylococci but that this power was very low. The low incidence of *Staph. citreus* in the sinuses is interesting, as the organisms could be recovered from the skin in approximately 20 per cent of these cases (*see below*).

The 21 strains of diphtheroid bacilli were next examined. One only was identified as *C. Hoffmanni*, the others being unidentifiable by the methods used. Eight strains were avirulent on testing. It was concluded that these organisms were either saprophytic or of low pathogenic power.

The fourth group of organisms isolated, 6 in number, were coliform bacilli. All were recovered from sinuses opening upon the lower abdominal wall, the groin, or the buttocks. They were *B. pneumoniæ* (Friedlander), *B. neapolitanus* (Emmerich) (3 cases), *B. proteus vulgaris*, and *B. rhinoscleromatis*.

Finally, there were the 5 unidentified organisms. Three were small Gram-positive bacilli and two were Gram-positive diplococci. They were all very friable and died out early in subculture.

These organisms occurred in the sinuses either alone or in combination with others. The commonest combinations were β-hæmolytic streptococci and staphylococci, followed by staphylococci and diphtheroid bacilli. β-hæmolytic streptococci in association with diphtheroid bacilli were seen rarely, the usual course being that when such streptococci were superadded to a sinus already infected with diphtheroid bacilli the latter disappeared. Coliform bacilli were always recovered in company with many other organisms. Staphylococci or β-hæmolytic streptococci were recovered often as the sole secondary infection in approximately equal proportion, whereas diphtheroid bacilli were rarely recovered alone. The secondary infecting organisms recovered from each sinus did not remain constant, but varied from time to time. When a β-hæmolytic streptococcus obtained ingress it proved to be the most persistent, and often the previous infection disappeared completely (*see Table III*). The most common early infection was by staphylococci alone. Sinuses which were healing or almost healed tended either to be free from secondary infection or to contain staphylococci in pure culture, even in sinuses where for a long period the secondary infection had been a β-hæmolytic streptococcus. Non-hæmolytic streptococci were commonly found in association with other organisms. These streptococci, staphylococci, and diphtheroid bacilli, and even coliform bacilli, were recovered always from sinuses in cases showing no clinical upset as a result of their presence. Where such clinical evidence of the presence of a secondary infection was noted, e.g., toxæmia, cellulitis around the sinus orifice, acute abscess formation in branches of the sinus, etc., the organisms recovered were β-hæmolytic streptococci, often alone and in great numbers or greatly preponderating over accompanying staphylococci. As the acute phase settled the streptococci decreased in numbers, and in the quiescent stage, if originally the sole infection, they were joined by staphylococci, which slowly preponderated, a feature also noted in instances where a few staphylococci were recoverable during the acute phase. Approximately 60 per cent of all the sinuses were infected with streptococci at some period in their course, and it was noted that the longer a sinus remained patent the more certain were these organisms to gain ingress.

Microscopically, secondary infection was present in the sinus exudates in the vast majority of cases, indicating that it was not a very minor feature, and that the organisms were recoverable only as a result of careful culture.

Out of 100 serial unselected smears of sinus exudate, 77 showed a secondary infection under the microscope, the incidence of the various organisms being: streptococci 58, staphylococci 31, diphtheroid bacilli 6, others 2, and tubercle bacilli 1. Streptococci were always a more gross infection than the others. The low incidence of tubercle bacilli is capable of explanation when it is considered that it was the free sinus exudate which was examined and not tissue scraped from the sinus wall, as was used when recovering the bacilli in culture. The sinus exudate in the presence of secondary infection was similar to that found in an acute inflammatory process, indicating that it arose in response to the secondary infection. The change in character of a sinus discharge from frankly tuberculous to acute inflammatory was noted repeatedly in lesions into which secondary infection gained entrance. This change was most marked in response to β-hæmolytic streptococci and little marked in response to staphylococci and diphtheroid bacilli. *Table III* illustrates these points. Note also the change in organisms recovered at different periods.

Table III.—Showing Change in Character of Sinus Discharge
(*Patient, A. McD.*)

Date of Examination	Infection Recovered				Cell Types of Discharge						
	Staph.	Strep.	Diph.	Others	Poly.	Mono.	Lymph.	Tissue Cells	R.B.C.	Phago-cytosis	Debris
Nov. 17, 1933	−	−	−	−	−	++	+	+	−	−	−
Dec. 1, 1933	−	−	+	−	+	+	+	−	++	−	+++
Feb. 1, 1934	−	++	−	−	+	+++	−	−	−	−	−
March 19, 1934	−	++++	−	−	+++	++	−	−	−	++	−
Nov. 10, 1934	++	+	−	−	++	+	+	−	++	−	−

The general conclusion was formed that the secondary infecting organisms in tuberculous sinuses were streptococci (mainly β-hæmolytic), staphylococci, diphtheroid bacilli, and coliform bacilli in that order numerically, and that the most active pathogens were the β-hæmolytic streptococci.

2. THE TIME OF ONSET AND MODE OF INGRESS OF SECONDARY INFECTION IN SINUSES

The Time of Onset.—A total of 57 patients with tuberculous abscess formation was observed in the following manner: Pus aspirated from the abscesses was examined bacteriologically, using the same technique as when recovering organisms from the sinuses. In all 188 specimens were examined, some abscesses being examined on one occasion only, others on numerous occasions. The greatest number of serial examinations in one case was twenty-three. The abscesses which were examined were grouped as follows:—

1. Those which were traced to breaking point or incision, 21 cases.
2. Those which healed without sinus formation or failed for other reasons to form sinuses, 27 cases.

3. Those which were in close proximity to secondarily infected sinuses, 6 cases.

4. Abscesses receiving an 'impetus' from the occurrence of scarlatina in the patient, 3 cases.

In the first group of 21 cases, 19 showed no bacteriological evidence of secondary infection prior to sinus formation. In 2 instances organisms were recovered: one was a groin abscess superficial in its later stages from which a small unnamed Gram-negative bacillus was cultured; the second was a small subcutaneous soft-tissue lesion of the lower calf from which a faintly β-hæmolytic streptococcus was recovered. In neither was there any clinical evidence of secondary infection, and in both the complete integrity of the overlying skin surface was doubtful.

In Group 2 every abscess examined, despite repeated aspiration in many cases, showed no evidence of any secondary infection.

Group 3. In 5 of the 6 cases the cultures were 'sterile', but in 1 an infection was present. The gland examined had almost eroded the surface and was adjacent to a sinus which was secondarily infected by staphylococci and β-hæmolytic streptococci. The organisms recovered were staphylococci and diphtheroid bacilli. There was no clinical evidence of such infection.

Group 4. These 3 cases, of whom brief clinical details are given, yielded negative results when the pus from their abscesses was examined for secondary infecting organisms:—

1. I. N., tuberculosis of dorsolumbar spine. Re-accumulation of pus in an abscess quiescent for previous eight months, seven days after the onset of scarlatina.

2. W. G., almost inactive tuberculous bone lesion of right hip. Fresh abscess appeared ten days after onset of scarlatina.

3. J. B., tuberculosis of sacrum. Abscess of thigh increasing greatly in size three days after onset of scarlatina.

These observations, added to the previously recorded fact that sinuses early in their course were commonly free from secondary infection, enable the conclusion to be made, under the conditions of the investigation, that tuberculous abscesses remain 'sterile' until sinus formation takes place. Also it may be said, in view of the findings in the third group of cases, that secondary infection in a sinus is strictly limited to the sinus track. Finally, although scarlatina occurring as an intercurrent disease gave apparent 'impetus' to a tuberculous focus in 3 instances over a total of 24 similar cases where it occurred, 21 showed no clinical or radiological change. It was concluded that the 'impetus' given by it was due to the cessation of normal treatment and to the increased movement of the injured part occurring while under treatment.

To determine when infection gained ingress after sinus formation had taken place 17 cases forming sinuses were examined at varying intervals, rarely exceeding fourteen days. *Table IV* shows when the sinuses formed and the date on which a secondary infection was first recovered, the third column showing the number of intervening days.

Infection almost invariably, but not necessarily, followed sinus formation, varying markedly in time, some being earlier infected than others. Over the entire investigation it was noted that sinuses free from secondary infection were rare after the first month of their course and that when it was absent from sinuses of longer duration they were healing.

Table IV.—Showing Time of Secondary Infection after Sinus Formation

Name	Site of Lesion	Date of Sinus Formation	Date of First Recovery of Secondary Infection	Interval
				Days
J. McG.	Glands (neck)	March 26, 1934	March 27, 1934	1
I. C.	Glands (neck)	Dec. 13, 1933	Dec. 16, 1933	3
W. L.	Left hip	Dec. 25, 1933	Feb. 10, 1934	47
M. B.	Right knee	Nov. 9, 1933	Feb. 1, 1934	84
P. T.	Left hip	Dec. 5, 1933	Jan. 12, 1934	38
J. McB.	Spine	Nov. 28, 1933	Jan. 10, 1934	43
R. McK.	Elbow	June 5, 1934	Healed uninfected	—
W. G.	Right hip	Feb. 19, 1934	Healed uninfected	—
	Reaccumulation	March 28, 1934	June 19, 1934	83
J. R.	Glands (neck)	Oct. 31, 1933	Healed uninfected	—
J. McL.	Left hip	June 1, 1935	Healed uninfected	—
M. G.	Spine	May 4, 1934	Healed uninfected	—
J. S.	Spine	Feb. 14, 1934	Feb. 14, 1934	—
H. McK.	Ankle	July 23, 1934	Oct. 13, 1934	82
J. G.	Femur	April 10, 1934	Oct. 21, 1934	184
J. G.	Ankle	June 18, 1934	Nov. 12, 1934	147
B. H.	Knee	Oct. 19, 1933	Nov. 17, 1933	29
		Nov. 9, 1934	Dec. 8, 1934	29

The Source of the Secondary Infecting Organisms.—In view of the data recorded regarding the nature of the infection, spread from the surrounding skin surface was the greatest possibility. Skin cultures were made in 21 instances and the following organisms were recovered: *Staph. aureus* 4 strains, *Staph. albus* 19 strains, *Staph. citreus* 5 strains, streptococci 2 strains (one hæmolytic, the other non-hæmolytic), and diphtheroid bacilli 7 strains.

This examination explained the source of staphylococci, diphtheroid bacilli, and, in view of the site of the sinuses infected with coliform organisms, coliform bacilli, but did not tend to indicate the skin surface as the source of the β-hæmolytic streptococci recovered from the sinuses in such a high percentage of cases. Other sources were examined. The first possibility was the spread of infection from sinus to sinus by faulty dressing technique; this did occur, and it was possible in the later stages of the investigation to prevent secondary infection occurring in a number of sinuses throughout their entire course by careful observation of surgical asepsis in dressing. The second possibility was droplet or air-borne infection. The behaviour of sinuses in the presence of intercurrent illness was noted and a close relationship between the recovery of β-hæmolytic streptococci from them and the occurrence of streptococcal throat infections amongst surrounding patients and staff was found to exist. The following are examples which were noted:—

1. Well-marked cellulitis appeared around an ankle sinus twenty-four hours after the patient in the neighbouring bed developed scarlatina. The only organism recovered from the sinus was a β-hæmolytic streptococcus eventually typed as *Strep. pyogenes*.

2. Marginal cellulitis around and an increase in discharge from a sinus occurred three days after a patient developed scarlatina. The secondary infection was a β-hæmolytic streptococcus in pure culture.

3. Cellulitis occurred in a recently formed, hitherto non-infected sinus arising from tuberculosis of the knee-joint within twenty-four hours of the patient developing scarlatina. The only organism recovered from the discharge was a β-hæmolytic streptococcus.

4. The patient in the neighbouring bed to the above case developed erysipelas migrans spreading from the mouth of a small sinus which had begun five days previously. It had

been sterile, yet the organism recovered in great numbers was again a β-hæmolytic streptococcus. This infection occurred sixteen days after the case of scarlatina had been isolated. The only common feature was the staff in attendance on them both.

5. Scarlatina appeared in one patient on Oct. 9, 1934. Increased activity occurred in the sinuses of his immediate neighbours, one on Oct. 6, 1934, the other on Oct. 13, 1934. In both instances the organisms recovered from the discharge were β-hæmolytic streptococci.

6. An example similar to the above was noted in another ward. Streptococcal throats occurred amongst staff and patients on the 1st, 2nd, 8th, and 17th of a month. On the 17th, 23rd, and 29th 3 frank cases of scarlatina were isolated, one nurse and two patients being affected. Increased activity in discharging sinuses, associated with the presence of β-hæmolytic streptococci in numbers in the discharges, was noted, commencing on the 3rd, 8th, 12th, and 19th. Streptococci were recovered, and as they had not previously been isolated from these sinuses it was inferred that they had gained ingress by droplet infection.

Based on these results, a conclusion was formed that secondary infection occurred after sinus formation and that it did not occur on aspiration of tuberculous abscesses. Also that the infection when it occurred gained ingress from the surrounding skin or from faulty dressing technique in the case of staphylococci, diphtheroid bacilli, and coliform bacilli, but that the streptococci, where they were capable of local pathogenic action, were conveyed either by droplet infection or as the result of transfer from a neighbouring streptococcal infected sinus due to faulty dressing technique.

3. THE CLINICAL EFFECT OF SECONDARY INFECTION

These observations were made on the cases whose sinuses were examined bacteriologically, but as secondary infection was present in only 90 per cent of the *sinuses* the number of cases in this section was reduced to 98. The majority of the cases were under clinical observation for all or the major part of their illnesses.

Many of the cases progressed apparently undisturbed by the presence of the added infection. Others, however, showed marked local and general upset. These upsets were often of a temporary nature, the patient following an apparently normal course after they had disappeared. Where the patient showed no clinical evidence of the presence of secondary infection the organisms recovered were staphylococci, diphtheroid bacilli, or non-hæmolytic streptococci, either alone or in combination, or some of the few unidentifiable organisms. Where clinical signs of infection were noted β-hæmolytic streptococci were always isolated from the sinuses. Thus when a sinus previously clinically quiescent and infected by staphylococci or diphtheroid bacilli, began to exhibit signs of infection, it was certain without bacteriological examination that it was now infected with streptococci. The action of coliform bacilli could not be defined as they were never cultured apart from streptococci.

The clinical sign most common was general toxæmia, with a marked increase in the discharge from the sinus. Less common was cellulitis of the soft tissues through which the sinuses ran, resulting often in abscess formation and fresh sinus formation, thus increasing the tissues involved in the tuberculous infection. Spread of infection from the sinus mouth to involve the surrounding skin was not uncommon, a local cellulitis resulting. Erysipelas migrans involving an entire arm and an entire leg was noted on two occasions. Lymphangitis occurred once

only, and acute lymphadenitis was seen on two occasions only. Surgical scarlatina was noted once. All these complications were associated with a secondary infection of the sinus by β-hæmolytic streptococci.

These complications caused an additional deterioration in the patients' general health outwith the action of the tuberculous lesion, and at times were felt to exercise an action on the latter. Thus the clinical notes made were designed to answer the following questions: The effect of secondary infection upon (1) the local spread of the tuberculous process, (2) the general spread of tuberculosis, (3) the activity of the tuberculous lesion, (4) the general health of the patient, (5) the hospitalization of the patient, (6) the healing of sinuses and their recurrence, and (7) the prognosis of each case.

1. Effect on the Local Spread of the Tuberculous Process.—Spread was deemed to have occurred when, following cellulitis or other inflammatory reaction, fresh surrounding tissues were infected by tuberculosis. Such spread took place mainly to surrounding soft tissues, but in some instances, particularly in the knee-joint and ankle-joint, fresh bone spread was felt to be due to it. It took place in the following incidence in each site: (*a*) Vertebræ, 6 : 22; (*b*) Hip-joint, 8 : 16; (*c*) Knee-joint, 4 : 7; (*d*) Ankle-joint, 7 : 7; (*e*) Long bones, 4 : 11; (*f*) Dactylitis, 4 : 12; (*g*) Glands, etc., 2 : 14; (*h*) Miscellaneous, 0 : 9. Fresh bone spread was noted only in the knee- and ankle-joints, in 2 and 3 cases respectively.

2. Effect on the General Spread of Tuberculosis.—Difficulty was experienced in assessing this factor, but in the light of clinical experience of similar cases it was thought to have been due to the action of secondary infection stimulating the activity of the primary focus and enlarging its field of action in two cases, viz., one hip-joint and one knee-joint.

3. Effect on the Activity of the Primary Focus.—An increase in this was also judged in the light of previous clinical experience, and occurred once only in each of the following sites: hip-joint, knee-joint, and dactylitis.

4. Effect on the General Health of the Patient.—Sinus formation caused no appreciable change in the patient. Mixed infection when it occurred did produce a change, however, varying with two factors, viz., the nature of the secondary infection and the site of the primary lesion. Where the secondary infecting organism was other than a β-hæmolytic streptococcus no change was noted in the patient, but where the latter was present, particularly if in numbers, the resulting complications invariably reacted adversely in the patient, as shown in weight loss or at least failure to gain weight, loss of appetite, etc. The site of the primary lesion was also important, as the most marked reactions were seen where the sinuses arose from lesions of the vertebræ, hip-joints, knee-joints, and ankle-joints, in that order. The vertebral lesions were marked only when they produced psoas or dorsal sinuses, the general determining feature throughout being the area of soft tissue liable to infection. Thus short sinuses such as are usually found in relation to dactylitis, glands, long bones (e.g., tibia in the present series), and miscellaneous lesions, generally produced no effect on the patient even when infected by streptococci. Staphylococci and diphtheroid bacilli, as has already been noted, did not seem to cause even a local reaction. The effect of toxæmia, etc., was well shown in two cases of disease of the ankle-joint with heavy streptococcal infection where amputation was performed. Both had previously remained at a stationary

weight for at least six months before the operation. In the two months after operation they gained 5 lb. and 7 lb. respectively.

5. Effect on the Hospitalization of the Patient.—*Table V* shows the total number of days residence of patients without sinus formation compared with the duration of the sinuses alone in the cases under observation. The comparative figures were taken from all previous cases treated in the hospital in which this work was done. It is necessary to point out a fallacy, viz., tuberculosis of the knee-joint without sinus formation includes in many instances patients who were hospitalized after the disease was arrested in order to have orthopædic treatment, thereby markedly increasing their stay in hospital.

Table V.—Showing Effect of Sinus Formation on Period of Hospitalization

Cases with Sinuses			All Cases
Site of Tuberculosis	Duration of Sinuses	Approximate Average Duration of Sinuses	Approximate Average Residence
Vertebræ	2–10 yr.	4 yr.	$2\frac{2}{12}$ yr.
Hip-joints	$\frac{4}{12}$–6 yr.	$2\frac{1}{2}$ yr.	$2\frac{1}{12}$ yr.
Knee-joints	$\frac{7}{12}$–$1\frac{7}{12}$ yr.	1 yr.	$1\frac{7}{12}$ yr.
Ankle-joints	$\frac{8}{12}$–3 yr.	$2\frac{1}{2}$ yr.	$1\frac{6}{12}$ yr.
Long bones	$\frac{4}{12}$–2 yr.	$1\frac{1}{2}$ yr.	$1\frac{1}{12}$ yr.
Dactylitis	$\frac{6}{12}$–3 yr.	1 yr.	$1\frac{1}{12}$ yr.
Glands, etc.	$\frac{1}{12}$–$1\frac{5}{12}$ yr.	$\frac{6}{12}$ yr.	$\frac{8}{12}$ yr.
Miscellaneous	$\frac{4}{12}$–1 yr.	$\frac{5}{12}$ yr.	No comparable figures

6. Effect on the Healing of the Sinuses and Their Recurrence.—It has already been stated that secondary infection was rarely present in healing sinuses and in a few instances was represented by a small number of staphylococci, diphtheroid bacilli, or, very rarely, friable non-hæmolytic streptococci. Such findings were irrespective of the nature of the previous organisms recovered, so that secondary infection was not a cause of persistence in sinuses. Similarly, cultures taken early from recurring sinuses were free from secondary infection, showing that it did not cause recurrence. A survey of 43 cases of bone disease with sinuses which had healed revealed the interesting fact that in 30 instances the sinuses healed within a few months of the underlying bone lesion becoming inactive clinically and radiologically. In 1 instance a sterile sinus remained patent for one year after healing of the primary focus. In 12 instances the sinuses healed shortly before the primary focus, and in 8 the healing was firm. In 4 cases recurrence took place, firm healing occurring later only after the underlying focus had become inactive.

7. Effect on the Prognosis.—This varied according to the site of the primary disease. *Table VI* compares the results of treatment in the cases under observation with the results obtained in similar uncomplicated lesions.

These clinical observations may be summed up by saying that sinus formation plus secondary infection, although only by β-hæmolytic streptococci, is a most serious complication. The local and general spread of tuberculosis may be aided and the activity of the primary lesion may be stimulated. The general health of the

patient is adversely affected, particularly in lesions of the vertebræ, hip-, knee-, and ankle-joints. Hospitalization of the patient is increased in lesions of these last-named parts, as well as of the long bones. The prognosis in general is worsened, the only exception being disease of the long bones. No form of secondary infection delays the healing of sinuses or plays any part in their recurrence.

Table VI.—Comparative Results in Simple and Secondarily Infected Cases

Site of Disease	Cases with Secondary Infected Sinuses						Uncomplicated Cases			
	No. of Cases	Died	Worse	No Change	Improved	Healed	No. of Cases	Died	Irregular Dismissals	Healed
Vertebræ	22	6	4	4	2	6	73	10	2	61
Hip-joint	16	2	2	1	2	9	64	3	1	60
Knee-joint	7	1			1	5	33	2	—	31
Ankle-joint	7	—	—	—	—	7	22	—	—	22
	(Two amputations necessary)									
Long bones	11	—	—	—	4	7	8	—	—	8
Dactylitis	12	1	—	—	3	8	20	3	—	17
Glands and soft tissues	14	1	—	—	—	13	60	2	—	58
Miscellaneous	9	1	—	—	1	7	No comparable figures			

SUMMARY

An investigation of 132 patients suffering from non-pulmonary tuberculosis with either abscess or sinus formation was made over a period of years and the following observations were made :—

1. Tuberculous abscesses remained free from secondary infection until the overlying surface was either eroded or abraded.

2. A secondary infection was present in 90 per cent of all the sinuses examined, the organisms most commonly found being streptococci, staphylococci, and diphtheroid bacilli, in that order.

3. Secondary infection gained ingress to the sinuses at varying periods of time *after* their formation.

4. The sources of secondary infection were : (*a*) the surrounding skin, (*b*) faulty dressing technique with spread from other infected sinuses, and (*c*) droplet infection. Sources (*a*) and (*b*) gave rise to staphylococci, diphtheroid and coliform bacilli, and streptococci ; (*c*) appeared to be prominently associated with β-hæmolytic streptococci.

5. Secondary infection in sinuses varied in its clinical effect on the patient. Excluding coliform bacilli, whose separate action it was impossible to estimate, organisms other than β-hæmolytic streptococci appeared to have little or no effect upon the patient.

6. Infection by β-hæmolytic streptococci was found to render the prognosis in each instance more grave. Hospitalization was generally increased and the general health of the patient was adversely affected. Also the local and general spread of tuberculosis may be aided and the activity of the primary focus stimulated.

7. The secondary infecting organisms were found to be, as a general rule, closely confined to the sinus track.

8. Sinuses were shown to heal in direct relation to the healing of the underlying focus of disease. Secondary infection, irrespective of its nature, was found to have no action in preventing their healing or causing their recurrence.

Briefly, therefore, the most active secondary infecting organisms, β-hæmolytic streptococci, were governed in their effects in direct proportion to three factors, the activity, the extent, and the duration of the tuberculous processes producing the sinuses.

In conclusion I wish to thank Dr. J. A. Wilson, the Medical Superintendent of Mearnskirk Hospital, Newton Mearns, Renfrewshire, where this investigation was carried out, for his constant guidance and encouragement during its entire course.

A CASE OF PERSISTENT INTUSSUSCEPTION IN AN ADULT

By N. F. KIRKMAN, Manchester

WITH AN ANATOMICAL NOTE

By T. BARLOW and S. MOTTERSHEAD
late house surgeons at ancoats hospital, manchester

The case reported is of interest because the condition had persisted since childhood. Intussusception in adults is not common. Most of the cases occurring after childhood are the result of a tumour of the small intestine, and in these cases symptoms usually become acute and the condition is discovered at operation.

Intussusception is usually an acute illness of childhood. W. S. Perrin and E. C. Lindsay[3] reported 18 adults in a series of 400 cases. In this series 78 per cent occurred in children under two years.

H. W. Goodall,[1] in an account of chronic intussusception in adults and a review of the literature of the subject, states that 21 recorded cases lasted more than four years, and of these 21 cases 4 were treated surgically, all except one dying from peritonitis. Since that date intussusception has been more frequently diagnosed in its earlier stages, with the result that for intussusception to persist from infancy to maturity is distinctly rare (H. Koster,[2] W. S. Perrin and E. C. Lindsay,[3] and A. J. Walton[4]).

CASE REPORT

History (September 20, 1939).—The patient was a female aged 44. She was married. She complained of abdominal pain, nausea, and loss of appetite. As long as she could remember she had suffered from periodical abdominal colic and a 'dropped' bowel. The colic had occurred at intervals of three months since 1933. It started about an hour after food in the right side of the abdomen, and radiated across to the left. It never occurred at night. The present attack of pain was more severe than former attacks, and for the last year the patient had suffered from diarrhœa. She had noticed blood and mucus occasionally in her motions. She passed a considerable amount of wind per rectum. During attacks her appetite was poor and she felt tired and listless. Between attacks, however, she was energetic and felt well. She had lost 1½ st. in weight during the previous year. Her menstrual periods were regular. In 1933 she had an appendicectomy for her complaint, but this produced no improvement.

The present attack started one month ago. She stated definitely that this was the worst attack she had experienced.

Family History: None of her brothers or sisters had suffered from any abdominal complaint.

On Examination.—The patient was a thin woman of average height, with a fair complexion and quite mentally alert.

Tongue: Smooth, clean and moist, faintly suggestive of achlorhydria.

Teeth: Complete dentures.

Heart: Size normal. Sounds normal, with tachycardia. Pulse-rate, 110.

Blood-pressure : 120 systolic, 75 diastolic.

Lungs : Normal.

Thyroid : Within normal size.

Abdomen : No abdominal masses palpable ; liver not enlarged.

Rectal examination showed normal fæces in rectum. The rectal mucosa bled rather easily when scratched.

Central Nervous System : The pupils reacted normally to light and accommodation. Knee-jerks, ankle-jerks, and plantar responses normal.

X-ray Report (September 25).—" (1) The barium enema flowed freely with no evidence of obstruction. (2) The whole colon was distended, i.e., a certain amount of megacolon was present. (3) The lower cæcal pole was not fully filled with barium and was slightly tender. Query post-operative adhesions."

Test Meal (September 26).—Gastric acidity within normal limits. No abnormality detected.

On Admission.—The patient was admitted to the wards of Ancoats Hospital on September 28, and sigmoidoscoped the next day by Mr. Peter McEvedy. The sigmoidoscopy showed a definite intussusception. The intussusception appeared while the examination was being conducted, but disappeared when the sigmoidoscope was passed to its full extent. The apex of the intussusception was estimated to have been from 7 to 8 in. from the anus.

October 1 : After walking about in the ward the patient stated that " the bowel was down ". When she was examined it was found that the intussusception had appeared at the anus and was protruding about 4–5 in. The mucosa resembled small intestinal mucosa. Slight peristaltic waves passed along the protruding bowel and it partly receded into the anal canal spontaneously and was reduced with ease.

Operation (October 3).—Laparotomy and ileopelvic colostomy by Mr. Peter McEvedy. Under heavy percaine spinal anæsthesia the abdomen was opened through a right lower paramedian incision. An intussusception of the small intestine was found. The apex of the intussusception was palpable in the lower part of the pelvic colon and it could be pushed upwards about 6 in. Where the small intestine entered the colon there were definite old adhesions. The small intestine was quite fixed to the colon at this point. The colon and cæcum appeared to be normally situated. A lateral anastomosis was performed between the ileum about 3 in. proximal to its entrance into the cæcum and the pelvic colon below the intussusception, the two mesenteries, the pelvic mesocolon, and small gut mesentery being united by two purse strings. The abdomen was closed without drainage.

Progress.—The patient had colicky pain and intermittent diarrhœa following her operation. She also had a remittent temperature. She did not appear to receive much benefit from this short-circuit operation.

December 12 : A barium meal radiograph furnished the following details : " Most of the meal has passed directly through the anastomosis to the rectum and has been completely evacuated at twenty-four hours. Some of the barium has gone through the colon and is seen to lie in the space between the invaginated small bowel and the outer wall of the colon, i.e., some sloughing has taken place and has allowed the barium to get through."

In view of these symptoms it was decided to perform a colectomy. The patient at this time was reasonably fit and her blood-count was as follows :—

Hb	60 per cent	W.B.C.	6000
R.B.C.	4,050,000	C.I.	0·74

Second Operation (December 19).—Hemicolectomy was performed by Mr. Peter McEvedy. Under nitrous oxide and oxygen and basal anæsthesia the abdomen was opened through a left paramedian incision through the old scar. The ileum was divided just beyond the ileopelvic colon anastomosis. The proximal end of the ileum was closed. The remaining distal ileum, about 3 in. long, and the proximal colon as far as the junction of the middle and proximal third of the transverse colon were mobilized and their peritoneal attachments divided. Owing to the broad mesentery of the small intestine entering with the intussusception, the removal of the lower part of the colon was difficult. The cæcum and colon were hypertrophied. The freed proximal colon was brought out through the upper part of the wound. The parietal peritoneum was sutured to it where it passed through, and the wound below it was closed. By opening the cæcum as it lay outside the abdomen the intussusception

was withdrawn from the distal part of the colon. A clamp was applied to the transverse colon where it entered the abdomen and the surplus colon removed.

The small intestine forming the intussusception was about 3 ft. long, bluish in colour and congested, especially at its terminal part. The circulation of this part seemed to have been very poor. A considerable quantity of mucopus and fæces lay between the intussuscipiens and the wall of the colon.

SUBSEQUENT PROGRESS.—After the operation the patient continued to have an intermittent pyrexia and occasional abdominal colic. She was given rectal washouts which were reported to be offensive. As her general condition after operation was poor it was decided not to sigmoidoscope her, but to wait for any abdominal inflammation to localize. M & B 693 (Dagenan) was administered for periods of two to six days, from 1·5 g. to 4·5 g. daily. Administration of large doses, or if it were continued over more than a few days, caused nausea and vomiting. Her weekly white-cell count never rose beyond 11,500 and was usually within normal limits, suggesting either a poor response to bacterial action or that there was no inflammation occurring, or possibly that the myelogenous bone-marrow was failing to respond to the presence of sepsis or that it was being adversely affected by the exhibition of sulphapyridine.

The Widal test was negative to typhoid, salmonella, and dysenteric organisms and the blood-culture which was performed three times was also negative.

February 27, 1940: A hard tender mass in the right iliac fossa was noticed. It remained tender and did not appear to vary in size. A fortnight later a considerable quantity of pus was passed rectally and pus appeared in the daily rectal washouts. The patient stated that

FIG. 248.—Specimen as removed at operation with cord in lumen of the remains of the intussusceptum.

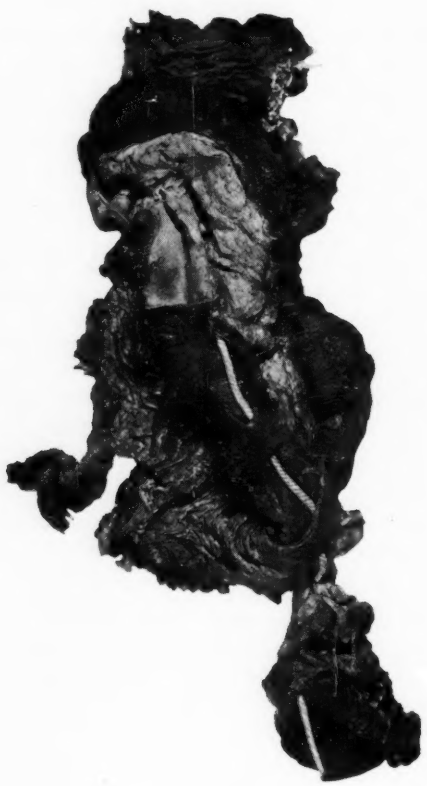


FIG. 249.—Intussusceptum opened to show the remains of the entering layer. (Q. R. in *Fig.* 254.)

she felt much more comfortable and her general condition began to improve. Her weight, which had fallen to 5 st. 8 lb., increased regularly week by week.

March 8: Sigmoidoscopy (Mr. Peter McEvedy). A small orifice on the right side of the rectum was found and from it pus could be seen running down. The orifice was situated near the rectosigmoid junction. Lower abdominal pressure increased the flow of pus.

March 28: The transverse colostomy was closed under local anæsthesia. The rectal washouts ceased to be offensive.

The patient continued to improve and was discharged on May 7, 1940.

ANATOMICAL NOTE ON THE INTUSSUSCEPTION

(T. Barlow and S. Mottershead)

The specimen was presented to us with the cæcum and ascending colon opened along their anterior aspects, with the intussusceptum lying in the lumen as shown in *Fig.* 248.

On introducing the finger into the lumen of the small intestine it was found to pass first posteriorly and then to bend anteriorly to enter the cæcum (at A in *Fig.* 253).

If this had been an ordinary intussusceptum one would have been able to trace the lumen of the intestine along the intussusceptum to the point P in *Fig.* 253, where there is a small polyp almost at the apex. It appears that part of the entering and returning layers of the intussusception had sloughed away on the antimesenteric border from the region of the ileocæcal valve to about 3 in. from the apex of the intussusception, i.e., between Q and A in *Fig.* 253. On closer inspection a groove could be seen between the points mentioned, with one small bridge of bowel wall (entering and returning layers) remaining at R (*Fig.* 253). On opening the intussusceptum a small tube of bowel wall was seen connecting the opening Q to the polyp at P, this being the remains of the entering and returning layers. *See Fig.* 249.

Figs. 250–253 illustrate the probable development of the condition from a simple ileocolic intussusception.

COMMENTARY

This case had evidently started as an acute intussusception in early childhood, although no definite history of a severe abdominal upset was forthcoming.

The passage between the ileum and colon had allowed normal alimentation to occur. This is very unusual. Goodall[1] reports in a review of the previous literature that 14 per cent of cases not operated on had recovered owing to complete sloughing of the intussusception. A. J. Walton[4] reports one case of spontaneous separation and cure in a series of 239 cases, and regards it as extremely rare. He states that in the majority of cases where no treatment is undertaken by far the greater number die through diffused peritonitis caused by intestinal leakage. Goodall, too, was only able to find 2 cases reported where a false opening had formed in the wall of the intussusceptum allowing free passage of the intestinal contents.

Since these dates a greater proportion of cases of intussusception have been operated on, so that cases of chronic intussusception have become increasingly rarer. The writer was unable to find a similar case recorded in the recent literature on the subject.

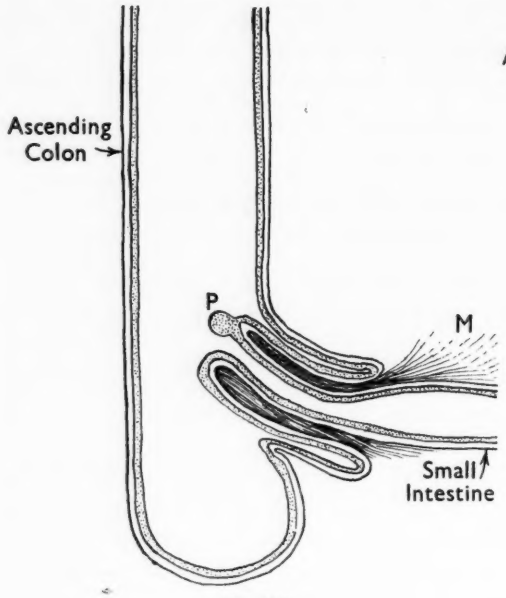


Fig. 250.

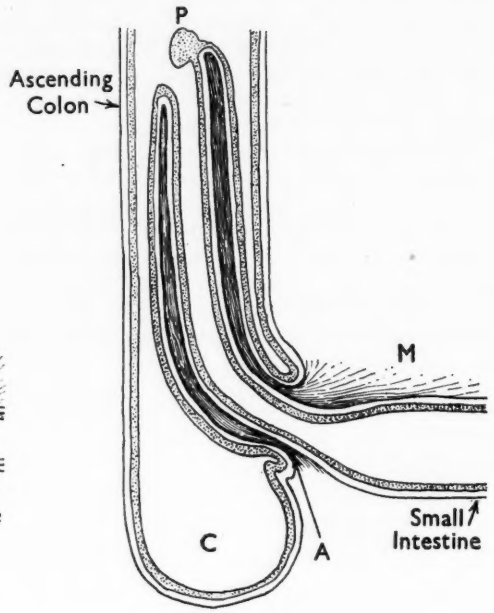


Fig. 251.

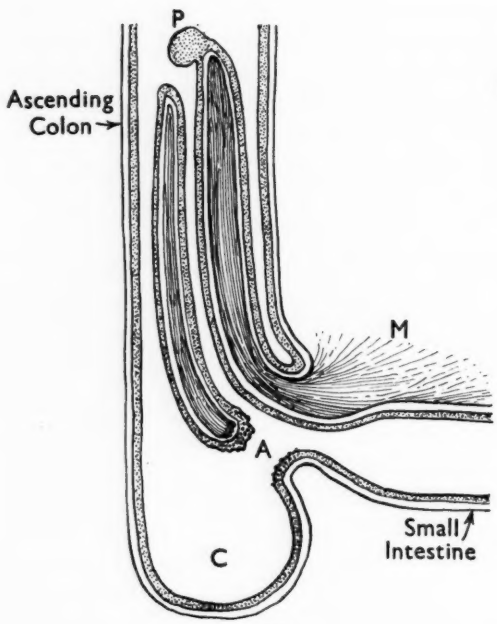
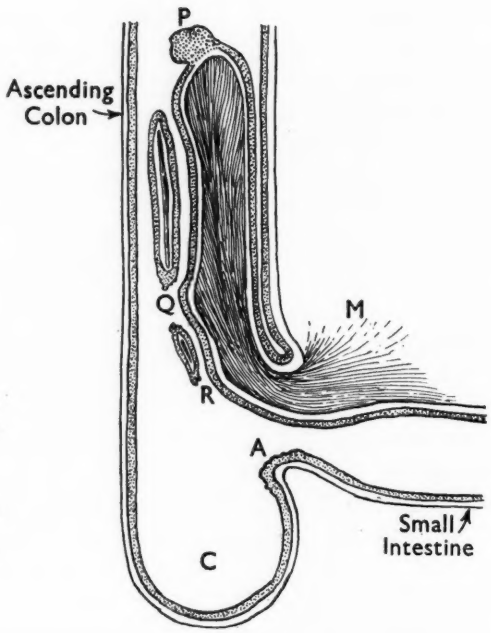


Fig. 252.



Fis. 253.

FIGS. 250–253.—Diagrams to illustrate the development of the intussusception seen in *Fig.* 248, showing how sloughing of entering and returning layers at points A and Q have led to this unusual condition.

SUMMARY

1. A case of chronic intussusception of many years' standing is reported.
2. Details of successful treatment by partial colectomy are given.
3. The formation of a false passage between the intussusceptum and the distal intestinal tract is discussed.

In conclusion thanks are due to Mr. Peter McEvedy, whose case this was, for permission to publish it; to Professor F. Wood Jones for his excellent reproduction of the anatomical diagrams; and to Mr. H. Gooding, Anatomical Laboratory Technician, for his photographs of the specimen.

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CARTILAGINOUS TUMOUR OF THE SHAFT OF THE ULNA

By T. VIBERT PEARCE and DOUGLAS H. COLLINS

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CASE REPORT

HISTORY.—Towards the end of August, 1936, the patient, a youth of 16 years employed as a clerk, was struck on the right forearm by a cricket ball while fielding. He continued to play. He cannot remember whether he was on the leg or the off side or whether he noticed a lump on his arm at once or when he got home, but he is sure that he noticed it for the first time that day, after the cricket. There was no bruising of his arm, but it was painful for a day. He continued to work.

On Oct. 14, 1936, he attended hospital. He had had pain in the right forearm for two weeks and difficulty in writing. On the back of the forearm there was a hard subcutaneous lump about 1 in. in diameter evidently growing from the shaft of the ulna at the junction of its upper and middle thirds. The mass was neither tender nor hot, nor was there any change in the colour of the overlying skin. Full pronation of the wrist was limited by about 45° in such a way that he could not write with comfort. He appeared to be well in every other way. There were no other bony lumps. A radiograph taken on this date showed a rarefied tumour expanding the cortex of the ulnar shaft on its dorsolateral aspect (*Fig.* 254).

FIG. 254.—Anteroposterior radiograph of right upper forearm with tumour, Oct. 14, 1936.

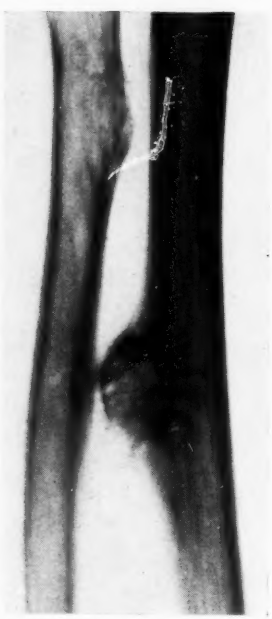

FIG. 255.—Anteroposterior radiograph, Dec. 4, 1936, showing increase in size of the tumour in seven weeks and the appearance of outlying spicule shadows.

FIG. 256.—Anteroposterior radiograph of right upper forearm, Jan. 10, 1940, three years after excision of tumour.

ON ADMISSION.—The patient was admitted to the Harrogate General Hospital on Dec. 4, 1936, and a further radiograph showed a considerable increase in size of the tumour and distinct shadows suggesting the formation of bony spicules outside the original contour

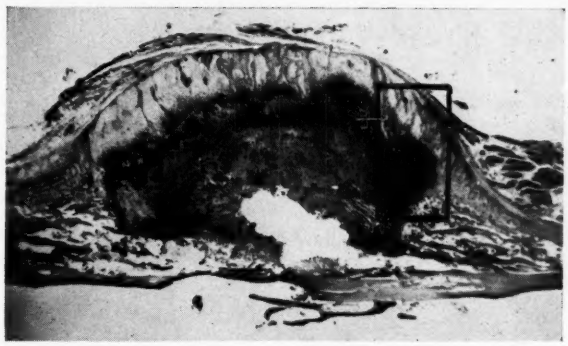

FIG. 257.—Longitudinal celloidin section of tumour, stained hæmatoxylin and eosin. The dark mass of cartilage growth is seen expanding the original cortical bone. There is cystic degeneration of the centre of the tumour but no penetration of the growth to the marrow cavity, which is the space at the foot of the picture. New bone trabeculæ are to be seen descending from superficial periosteum towards the cartilage growth. (× 2·4.)

FIG. 258.—Higher-power view of the area outlined in *Fig.* 257, showing invasion of original bone by the edge of the cartilaginous tumour. Stained hæmatoxylin and eosin. The unusual appearance of the neoplastic cartilage is peculiar to the celloidin technique. It is due partly to the section being somewhat thick, but mainly to the absence of shrinkage of the cartilage cells. (× 44.)

of the expanded cortical bone (*Fig.* 255). Clinically the tumour now measured about 1¼ in. in diameter. The patient was unable to write properly and complained of stiffness in the fingers, but there were no definite signs of nerve involvement.

AT OPERATION.—On the same day the tumour was easily enucleated from the extensor muscles of the thumb, outlined above and below by saw cuts, and struck off gently with a chisel.

PROGRESS.—On Dec. 15, 1936, the patient could sign his name more easily. Improvement in writing was steady and two weeks later he returned to his work.

In August, 1937, he was examined and no disability whatever existed. Remodelling of the ulnar cortex was shown radiographically. Radiographs of the chest showed nothing unusual.

In January, 1940, more than three years after the excision of the tumour, the patient was again examined. He was in perfect health. A radiograph of the forearm showed accurate restoration of bone at the site of the excision and no suggestion of recurrence of the tumour (*Fig.* 256).

Pathological Description of the Tumour.—The gross specimen consisted of a piece of cortical bone on which lay a hard sessile ovoid tumour measuring $\frac{1}{2} \times \frac{3}{4} \times 1$ in., the long axis of the tumour lying in the line of the bone shaft. The specimen was divided longitudinally and decalcified. Half was embedded and cut in celloidin and the other half in paraffin.

The large celloidin section (*Fig.* 257) shows the general structure of the tumour. The cortical bone is expanded on either side to enclose a cartilaginous mass the bulk of which is formed of cartilage cells of adult type packed closely together and roughly arranged in columns radiating outwards from the centre of the deep part of the tumour, which has undergone cystic degeneration. Superficially this dense adult cartilage merges, through an ill-defined zone of cartilage of fœtal type, into a myxomatous connective tissue with stellate cells. This in turn gives place to a collagenous fibrous tissue. Cortical bone does not completely cover the tumour. Its free surface is bounded by fibrous periosteum from which delicate bone trabeculæ of apparently new formation descend to meet the tumour cartilage. They are outlined for the most part by a regular layer of osteoblasts. The growing mass of cartilage forming the bulk of the tumour is seen to be invading the expanded cortical bone at either side (*Fig.* 258), but there is no invasion through the deeper strata of the bony cortex of the shaft into the marrow cavity.

DISCUSSION

At the first clinical and radiographic examination this tumour was thought to be a benign osteochondroma, but the rapidity of its growth in the seven weeks between the first and second examinations, as well as the increasing disability due to its presence, rendered its removal expedient. Pathologically the tumour differs from osteochondroma or exostosis in the absence of tendon attachment at its site and in the reversed relation of bone to cartilage, the ordinary osteochondroma possessing a superficial cap of cartilage. The tumour lay towards the centre of the shaft at a distance from the epiphysis which is unusual in the benign chondromata and also in chondrosarcomata (Phemister, 1930). McMaster (1935) has suggested that cartilaginous inclusions resulting from previous rickets might originate tumours at a later date, and he has shown such inclusions to persist in the cortex of the metaphysis of long bones, but there was no evidence that our patient had ever been rachitic.

Microscopical examination still leaves the diagnosis of malignancy in some doubt. The lateral invasion of cortical bone by neoplastic cartilage and the presence of a relatively undifferentiated fœtal type of cartilage and myxoid tissue are suspicious, and yet atypical mitoses, which, as Keiller (1925) stated, are the absolute microscopical proof of malignancy, are absent. Malignant transformation of a previously benign cartilaginous tumour may occur at any time. In discussing the new classification of bone tumours by the Bone Sarcoma Registry of the American College of Surgeons, which now includes a separate group of tumours derived from and producing cartilage, Ewing (1939) points out that there are all

grades of malignancy of these growths. Geschickter (1931) says that the relationship and the origin of the benign and malignant forms of cartilage tumours of bone are so nearly identical " that it is often impossible, even with all the data at hand, to predict whether the outcome of the growth will be benign or malignant ". Our considered opinion on the tumour we have described is that, though probably benign in origin, malignant transformation was commencing in it at the time of its excision. After three years without any sign of recurrence we hope that the episode is closed.

The patient attributed the lump to the blow from a cricket ball, but close scrutiny of his story suggests that the mass may have been present already at the time of the accident. The trauma may have accelerated its growth. Meyerding (1939) noted a history of trauma in some 45 per cent of his cases of osteogenic sarcoma, but its influence on tumour growth cannot yet be assessed.

The rarity of cartilaginous tumours of the ulna is a further point of interest in this case. In a series of 488 fibrocartilaginous tumours of bone reported by Geschickter (1931), only 4 originated in the ulna, and only 1 of these, a primary chondrosarcoma, occurred in the shaft of this bone.

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THE ROLE OF VITAMIN C IN WOUND HEALING

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THE biological factors of wound healing have received surprisingly little attention from surgeons, although great pains have been taken to give wounds every possible mechanical advantage in the form of expert surgical technique. Migration and proliferation of epidermal and mesodermal cells, the production of an intercellular matrix, and the formation of new blood-vessels are the essence of wound healing. This process, as Carrel has recently remarked, is the most fundamental in surgery, and yet most wounds are left to look after themselves. Clean sutured wounds will heal satisfactorily as a rule, but there are occasions when they inexplicably break down in spite of the most meticulous attention at operation. In these cases there is usually evidence of a nutritional deficiency affecting the proliferating powers of the cells or the capacity of the mesodermal cells to lay down intercellular substances.

Cellular Proliferation.—Cellular proliferation begins after a latent period of a few days[16, 22] and is accompanied by active phagocytosis of tissue which has been damaged or rendered functionless by the incision. The cells, fibroblasts in the case of soft-tissue scars, proliferate and migrate amongst the fibrinous strands which alone complete the sealing of the gap during the preliminary one to four days of wound healing, and they are accompanied in their growth by budding blood-vessels. The severed edges of the wound are thereby joined by a granulation tissue which has formed in response to the stimulus of damaged cells. A normal rate of cellular proliferation is essential to the formation of the scar. It varies with age and is dependent to a considerable extent upon the protein content of the blood. This was first shown by Clark[8] and confirmed by Thompson, Ravdin, and Frank,[40] who demonstrated that there was not only a delay in the appearance of new fibroblasts but also a slowing up of their multiplication in experimental hypoproteinæmia. Complementary experiments were carried out by Harvey and Howes,[17] who showed that the proliferation of fibroblasts could be speeded up by feeding with a high protein diet.

Little is known about the substances which initiate the proliferation and migration of epithelial cells and fibroblasts. Arey,[3] in reviewing the whole problem of wound healing, discusses the various theories and concludes that the most effective stimulants are embryonic juices, substances containing the sulphydril radical, and products of cell disintegration. It is possible to make practical use of these discoveries in the case of open wounds, for example, in the application of amniotic fluid or sulphydril compounds to stimulate epithelialization. But there is no known substance that can be administered internally or parenterally for the purpose of stimulating the proliferation of mesodermal cells in closed wounds. The correction of hypoproteinæmia can only be considered a healing stimulus in that an inhibition has been removed. That common substances may inhibit fibroblastic proliferation has been shown by Heaton[18, 19] and Medawar[31], who found that certain extracts of malt and a number of mammalian organs produce this effect even when taken by mouth.

Deposition of Collagen.—The strength of a scar is dependent on the intercellular substance laid down by the fibroblasts and the full maturation of this substance, precollagen, to collagen. Effective and rapid deposition of collagen is the essential process in scar formation, but it is well to recognize that this process is, in the first place, itself dependent on the proliferation of mesodermal cells. Callus is formed in the same way, the osteoblasts laying down osteoid tissue which matures to bone. In the past it had been supposed that collagen arose either by transformation of the fibrin or from the fibroglia of the cell-protoplasm itself, but it is now more generally accepted that it arises as a condensation of the extracellular material in immediate association with the fibroblasts and their processes. The production of this material and its maturation to collagen can be followed out histologically by a combination of two methods :—

1. In sections impregnated with silver, the intercellular substance laid down around the newly proliferating fibroblasts is at first clearly demonstrable as coarse irregular black fibres. This capacity to take up silver disappears rapidly during the process of maturation, the fibres becoming brown, and then, in about 10 to 14 days from the suture of the wound, a translucent yellow.

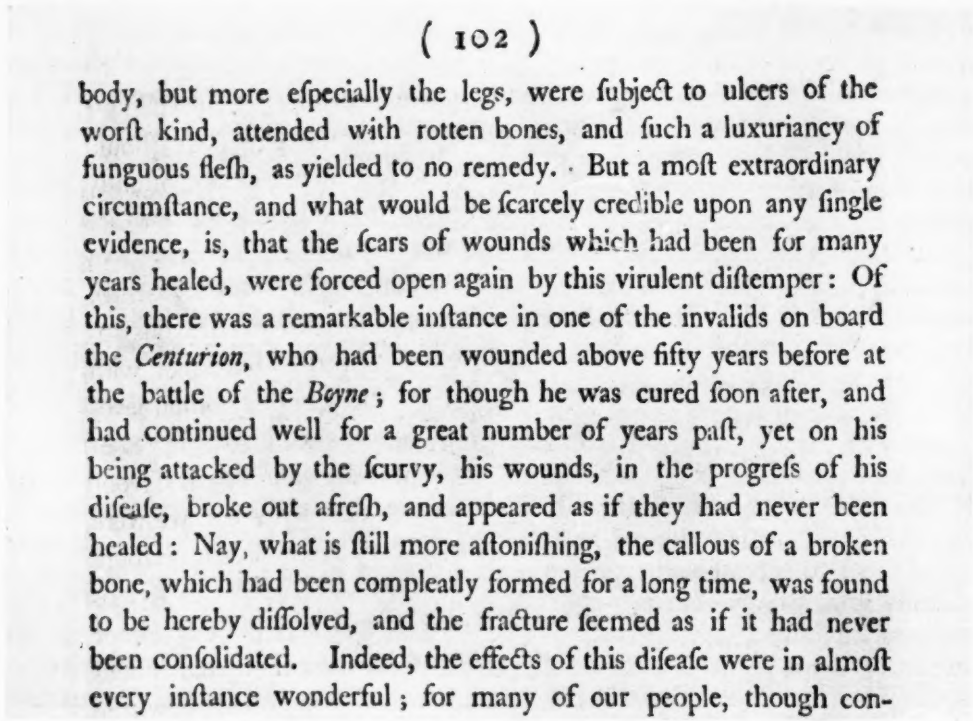
2. An affinity for van Gieson's stain develops while the capacity of the fibres to stain with silver is being lost. Thus, by the sixth day, some of the precollagenous fibres, brown to silver impregnation, are pale pink with van Gieson ; by the tenth day they will be almost indistinguishable in colour from mature fibrous tissue.

These reactions of normal healing may be expressed in graphic form, as in *Fig.* 261. This representation of the healing process is not intended to be mathematically accurate, since it is based on histological observation, supported by the conclusions of other workers such as Howes, Sooy, and Harvey.[22] However, the staining methods serve as a reasonably accurate estimate of the speed with which the fibroblasts are laying down intercellular material, the maturation of this material to collagen, and, therefore, of the development of the holding power of the scar.

THE RELATIONSHIP OF VITAMIN C TO COLLAGEN PRODUCTION

It has long been known that wounds heal poorly in scurvy. The classic account by Anson[1] in 1748 is reproduced in *Fig.* 259. James Lind,[27] in 1772, refers often to this aspect of scurvy. " Whereas, when one has been confined from exercise by having a fractured bone, or from a bruise or hurt, these weak and debilitated parts become almost always first scorbutic ". Describing the development of the disease, he says that " it is not unusual at this time, for such persons as have had ulcers formerly healed up to have them break out afresh ". A Dr. Grainger, writing to Lind concerning scurvy (" a subject of which I had read much, but knew little "), also describes how old ulcers broke out again. In 1919 Aschoff and Koch,[4] working on human material, showed that in scurvy there was always a deficiency in the formation of new intercellular substances and an inability to maintain established supporting structures. Höjer[21] demonstrated a general atrophy in collagen in scorbutic guinea-pigs. Wolbach and Howe,[41] Wolbach,[42, 43] and Menkin, Wolbach, and Menkin,[32] in a series of papers from 1926 onwards, have shown in guinea-pigs that reticulum and collagen are not formed in the absence of vitamin C or ascorbic acid. According to von Jeney and Törö,[24] ascorbic acid added to the culture medium

of explants of fibroblasts accelerated the deposition of intercellular substances, and they confirmed the observation of Doljanski and Roulet[10] that collagenous fibres could form in parts of the medium free from cells. Lanman and Ingalls,[26] in 1937, and Taffel and Harvey,[39] in 1938, have shown that the tensile strength of



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body, but more eſpecially the legs, were ſubject to ulcers of the worſt kind, attended with rotten bones, and ſuch a luxuriancy of funguous fleſh, as yielded to no remedy. But a moſt extraordinary circumſtance, and what would be ſcarcely credible upon any ſingle evidence, is, that the ſcars of wounds which had been for many years healed, were forced open again by this virulent diſtemper: Of this, there was a remarkable inſtance in one of the invalids on board the *Centurion*, who had been wounded above fifty years before at the battle of the *Boyne*; for though he was cured ſoon after, and had continued well for a great number of years paſt, yet on his being attacked by the ſcurvy, his wounds, in the progreſs of his diſeaſe, broke out afreſh, and appeared as if they had never been healed: Nay, what is ſtill more aſtoniſhing, the callous of a broken bone, which had been compleatly formed for a long time, was found to be hereby diſſolved, and the fracture ſeemed as if it had never been conſolidated. Indeed, the effects of this diſeaſe were in almoſt every inſtance wonderful; for many of our people, though con-

FIG. 259.—Photostat reproduction from p. 102 of *A Voyage Round the World*, by George Anson, compiled by Richard Walter, 1748.

healing wounds in guinea-pigs suffering from a partial deficiency of vitamin C is considerably less than in normal animals. It is supposed that ascorbic acid acts as an oxidation-reduction enzyme enabling the deposition of reticulum, collagen, bone, enamel, dentine, and possibly cartilage and elastin to take place. It has not yet been established whether the defect in vitamin-C deficiency is due to a failure of the process of gellation of the intercellular matrix[41] or to a degeneration of the specialized mesodermal cells of the supporting tissues.[12, 14, 29]

Vitamin-C Deficiency.—Scurvy is now a rare disease. Interest is centred on the state of partial deficiency know as ' sub-scurvy ' or ' asymptomatic scurvy ', though these terms should be accepted with reserve. The following figures for the ascorbic acid content of the blood given by Ingalls and Warren[23] roughly define this state :—

		Ascorbic Acid in mg. per 100 c.c. of Blood
Optimum :	Saturation	2·00–1·00
	Normal	1·00–0·70
	Low normal	0·70–0·50
Suboptimum		0·50–0·30
Deficiency :	Asymptomatic scurvy	0·30–0·15
	Scurvy	0·15–0·00

It has been shown in numerous papers[2, 5, 11, 13, 15, 23, 34, 37] that a state of partial deficiency exists in a high proportion of individuals, especially among the poorer classes. This is particularly so in patients suffering from diseases of the gastro-intestinal tract when the supply of vitamin C is inadequate from dietetic restrictions (e.g., in peptic ulceration) or from defective absorption of the vitamin (in carcinoma of the stomach or colon, or chronic intestinal obstruction from any cause). In acute or chronic infections, injuries (including operations), and in all malignant neoplastic diseases a higher intake of the vitamin is necessary to maintain a normal blood saturation than in the case of normal individuals.

INVESTIGATION

The present research was undertaken to elucidate further, by histological examination of wounds, the defects in the process of wound healing in guinea-pigs suffering from a partial deficiency of vitamin C. Bearing in mind the warning of A. F. Hess[20] that the guinea-pig is far more sensitive to scurvy than man and that " this prevents our carrying out delicate quantitive experiments and cautions against drawing too finely spun deductions ", an attempt was also made to discover whether these experimental findings could be applied to man.

The investigation was restricted to incisions of the abdomen and gastro-intestinal tract, because it is in gastro-intestinal surgery that dietetic deficiencies are most commonly encountered. Further, it is essential for these scars to heal rapidly and well so that they can withstand the strains and stresses to which they are often subjected. If they break down the consequences may be disastrous. They are, therefore, of particular interest.

A. ANIMAL EXPERIMENT

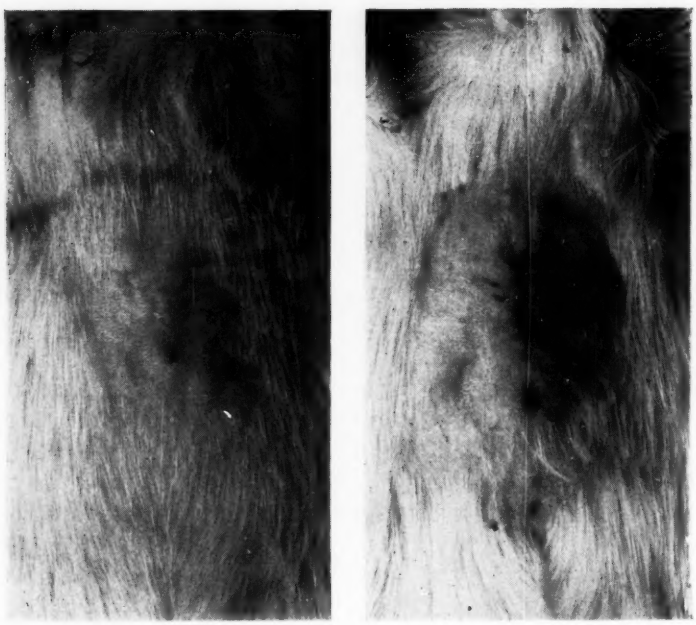
Twenty-four young virgin female guinea-pigs, weighing between 300 and 450 g., were given *ad libitum* a scurvy-producing diet[36] of whole crushed oats (59 per cent), full-cream milk powder heated to 110–115° C. for three hours (30 per cent), butter (10 per cent), and salt (1 per cent), to which was added iron and vitamins A and D. The animals were divided into two groups: 12, the controls, were given adequate doses of ascorbic acid (4 mg. on alternate days); and 12, the deficient group, were given only enough ascorbic acid to prevent the development of any objective sign of scurvy ($\frac{1}{2}$ mg. on alternate days, administration beginning on the tenth day of the experiment). The vitamin, freshly dissolved in $\frac{1}{2}$ c.c. of recently boiled distilled water, was given by pipette. The animals were operated on in pairs, one from each group, after they had been on the special diet for at least two weeks. The pairs were killed at intervals of 1, 2, 3, 5, 7, 10, 14, 17, and 21 days after operation.

The operation was done by a carefully standardized technique and with full aseptic precautions. The prepared abdominal wall was incised for 1 in. down from the xiphisternum and the peritoneal cavity opened. The stomach was partially delivered, clamped with a small rubber-covered clamp, and an incision half an inch long made into the lumen. This gastrotomy wound was closed with a continuous inverting suture of 00 plain catgut. The abdominal incision was closed in three layers, a continuous suture of 00 plain catgut for the peritoneum, interrupted finest silk sutures for the muscles and fascia, and a continuous finest silk suture for the skin. The wounds were covered with a temporary collodion gauze dressing. The animals were starved for 24 hours preceding operation except for the administration of

10 c.c. of 50 per cent glucose solution about 4 hours beforehand. They were allowed to feed immediately they had recovered from the anæsthetic, which was open ether.

When the animals were killed, the abdominal and gastric wounds were excised with as little surrounding tissue as possible, fixed in Bouin's fluid for 14 hours, blocked in wax, and sectioned. The sections were stained by four methods; hæmatoxylin and eosin, van Gieson's connective-tissue stain, Foot's modification of the Bielschowsky-Maresch silver impregnation method, and Mallory's connective-tissue stain. Section cutting and staining were done entirely according to a standardized routine so as to obtain exactly comparable pictures.

Macroscopical Findings.—All the wounds healed by first intention, in that there was no macroscopical infection. The wounds of the controls, in the earlier stages of healing, were less red, less thick, and showed less surrounding induration than those of the sub-scurvy animals, but the latter showed no greater tendency to bleed at operation. The scabs, in the case of the controls, came off earlier; the shrinking of their scars, both across and along the line of the incision, was greater; the final scars were almost invisible, pale, and projected slightly above the surrounding skin. In the sub-scurvy animals, on the other hand, they were puckered, stretched, sunken, and showed a mauvish discoloration (*Fig.* 260). The contrast



A B

FIG. 260.—Abdominal incisions of guinea-pigs, 21 days after operation. Life size. Both healed by first intention. A, Control animal; B, Sub-scurvy animal.

between these gross appearances was striking, and, apart from anything else, sufficient to distinguish the two groups of animals from each other. To the casual observer, on the other hand, the scars of the sub-scurvy animals appeared to be well healed, until compared with those of the control group.

Microscopical Findings.—

1. *Cellular Proliferation.*—Cellular proliferation was found to be little affected by a deficiency of ascorbic acid during the earlier stages of healing. New fibroblasts began to appear on the third post-operative day in both groups and then multiplied to about the same extent. In the controls this proliferation ceased on

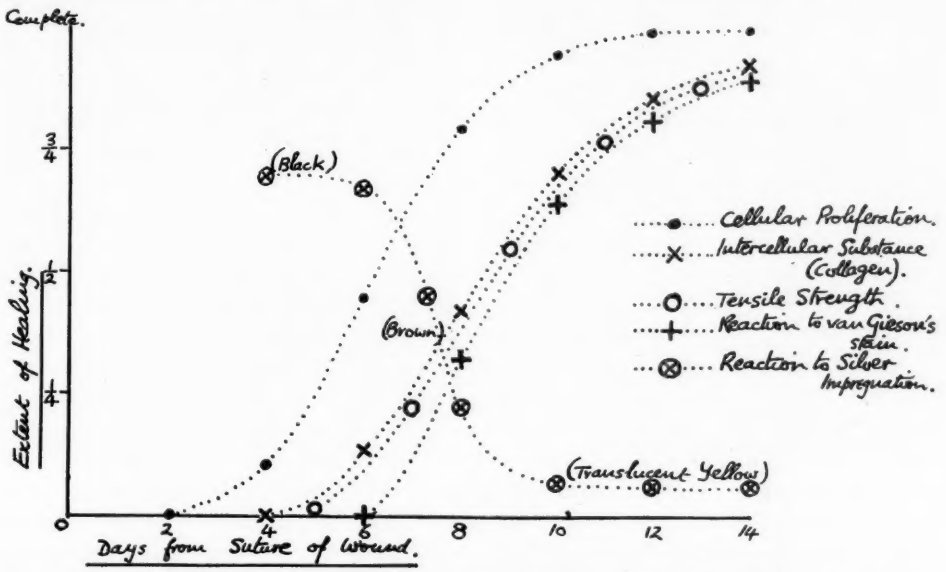


FIG. 261.—Graph to illustrate the approximate course of healing, with the staining reactions of the intercellular substance, of wounds in normal guinea-pigs.

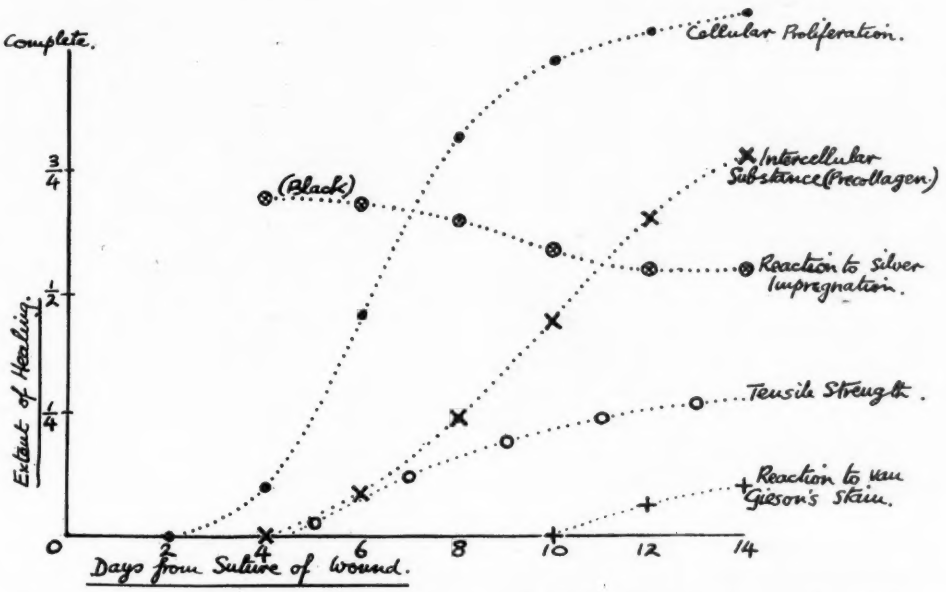


FIG. 262.—Graph to illustrate the approximate course of healing, with the staining reactions of the intercellular substance, of wounds in sub-scurvy guinea-pigs.

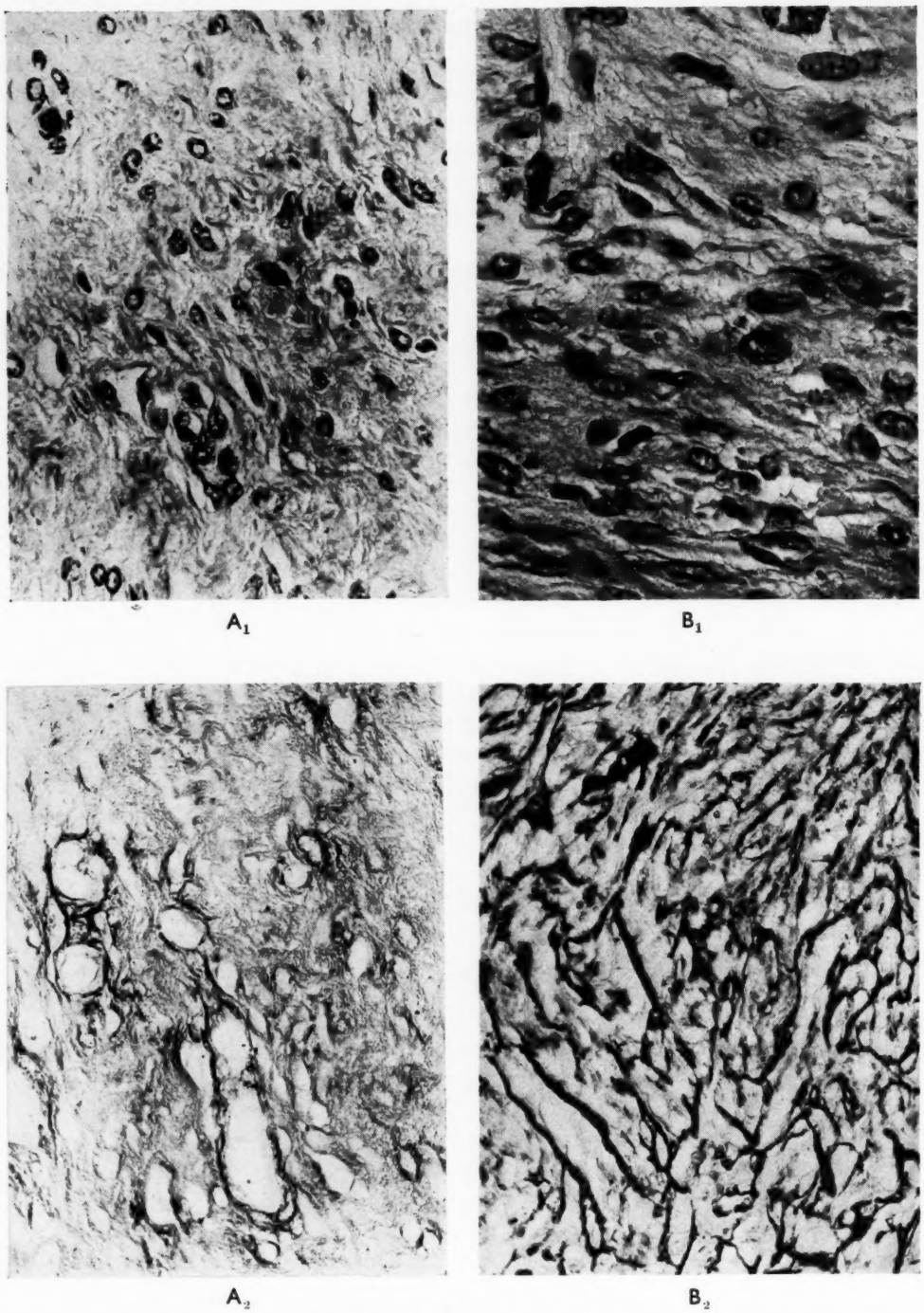


FIG. 263.—From the abdominal scars of guinea-pigs killed 21 days after operation. (× 400.) (Enlarged from *Fig.* 265.) A_1, A_2, Control animal; B_1, B_2, Sub-scurvy animal.

A_1, Fibrocytes. B_1, Fibroblasts (stain, hæmatoxylin and van Gieson).

A_2, Black, silver-staining reticulum fibres only around the blood-vessels. The intercellular substance is composed of mature collagen. B_2, Black, silver-staining precollagen forming the whole intercellular substance (stain, silver impregnation).

about the fourteenth day, when the scar was consolidating, whereas in the sub-scurvy animals it continued long beyond that time. This suggested that the lack of ascorbic acid actually stimulated the proliferation of cells. It is more likely, however, that fibroblasts will continue to multiply so long as there is need of the formation of scar tissue, and, if this formation is delayed, cellular proliferation will be prolonged (*Fig.* 262). The cells remain immature (*Fig.* 263). There was no difference in the production of 'foreign-body' giant cells around the sutures, but the mesodermal cells proliferating around damaged muscle-fibres produced more giant multinuclear forms in the sub-scurvy animals. The regeneration of epidermis and stomach epithelium was similar in the two groups, though more regular in the controls.

2. *Production of Intercellular Material.*—In the production of intercellular material there were great differences. In the controls, argyrophil precollagen was laid down in large quantities around the fibroblasts and was clearly demonstrable by the fifth day. Maturation to collagen began by the seventh day and progressed rapidly. In the sub-scurvy animals precollagen appeared a little later and in smaller quantities. It failed to mature and remained argyrophil in nature throughout the whole period of 21 days (*Fig.* 262). No van Gieson-staining intercellular substance could be seen in the 'scar' of the healed wound. *Fig.* 263 shows the difference between the intercellular substances in the two groups. In the control animal, A, black argyrophil fibres can be seen only around the capillaries. These fibrils are probably true reticulum forming the cement substance and basement membrane of the endothelial cells. The rest of the ground substance is dense collagen and appears a translucent yellow in the section. In contrast, the whole of the intercellular substance of the sub-scurvy animal, B, stains densely black with silver. It does not show the fine fibrillary nature of reticulum, but the coarse irregular strands of precollagen.

3. *Structure of the Wound as a Whole.*—In comparing the wounds of these two groups of animals, differences in the structure of the wound as a whole were quite as striking as the variations in the production of intercellular material.

a. Dermis: Where an incision passes through skin in a normal animal and there is accurate approximation of the cut surfaces, secure fibrous healing takes place across the full width of the corium, with little, if any, reduction in the final thickness of the skin (*Fig.* 264, A). This was well shown in the control animals. In the sub-scurvy animals, on the other hand, a small hæmorrhagic effusion appeared after a few days and gradually extended between the opposed surfaces so that the corium opened out internally. The skin became greatly reduced at the site of the incision, and finally, on the twenty-first day, consisted of little more than epidermis overlying ill-formed granulation tissue (*Fig.* 264, B). The final scar, therefore, appeared sunken and discoloured. Possible technical variations cannot be impugned for producing this effect, because the stretching of the scar could be traced through the successive stages of wound healing.

b. Scar: The scar itself in the controls was compact, uniform, and vascular throughout, composed of mature fibrocytes in a matrix of collagen. There was no effusion (*Figs.* 264, A and 265, A). In the sub-scurvy animals it was loose, irregular, and almost avascular, composed of fibroblasts in a matrix of precollagen (*Figs.* 264, B and 265, B). It was far more cellular and split up by extravasations of blood-stained fluid. These effusions continued to appear throughout the healing

and were bordered by fibroblasts and not capillaries. The few microscopic hæmatomata that could be found in the wounds of the normal animals were organized in the usual way by the ingrowth of blood-vessels followed by fibroblasts.

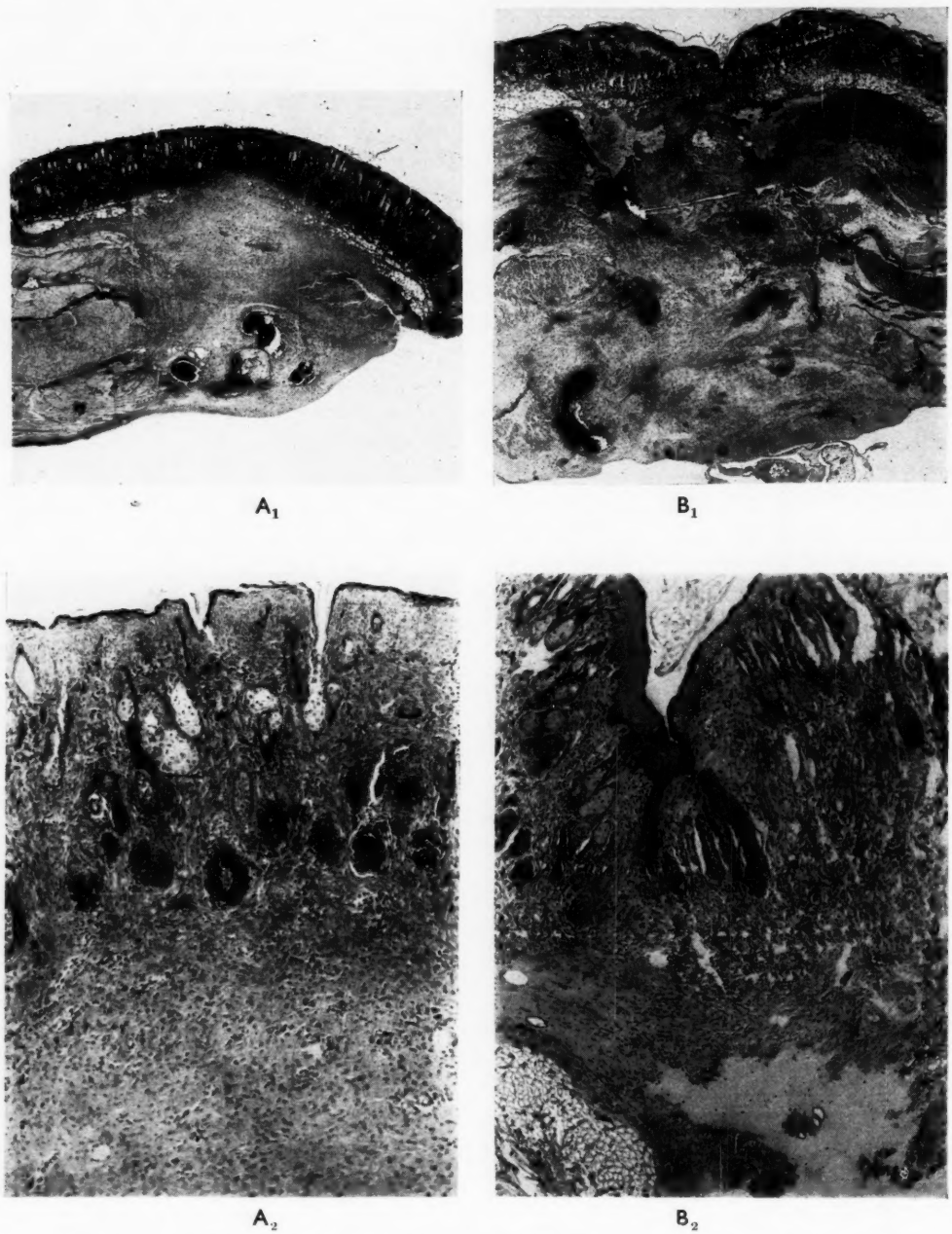


FIG. 264.— Cross-sections of the abdominal incisions of guinea-pigs killed 21 days after operation (stain, hæmatoxylin and van Gieson). A, Control animal; B, Sub-scurvy animal.

A_1, Dense, homogeneous, collagenous scar with corium of good thickness and without effusions; B_1, Soft, thick, œdematous, poorly-formed 'scar' with puckered, thinned-out corium and many effusions. (× 7.)

A_2 and B_2, The same (× 56). (Silk ligature bottom left in B_2.) Cf. *Fig.* 260.

c. Phagocytosis and absorption of damaged tissues and removal of catgut ligatures: An essential part of wound healing is the phagocytosis and absorption of damaged cells and the 'knitting-in' of remnants of tissues bordering on the incision. In the controls, this whole process had been completed by the twenty-first day and there was then no trace of aponeurotic strata extending through the uniform scar from the adjacent muscle layers (*Fig.* 264, A). In animals deficient in ascorbic acid, this reorganization and fusion of old and newly-formed fibrous tissue was long delayed. Remnants of intermuscular strata could be traced through the forming scars for a long time. *Fig.* 267 illustrates the abdominal

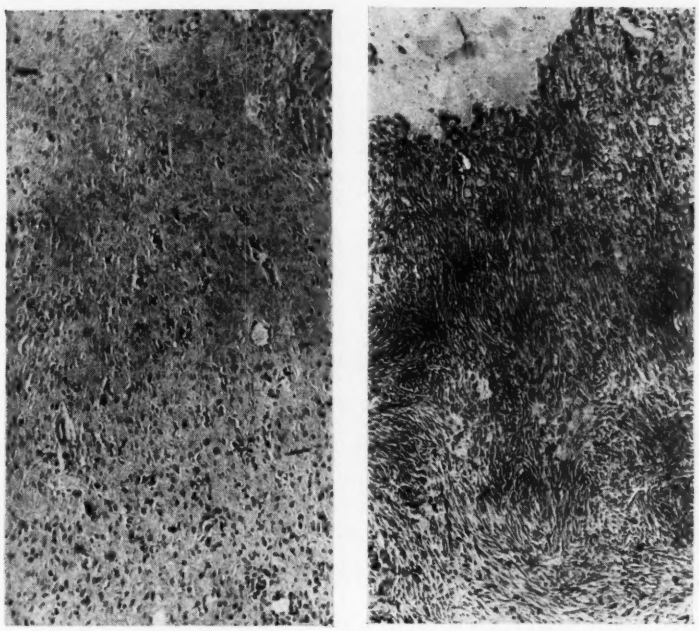
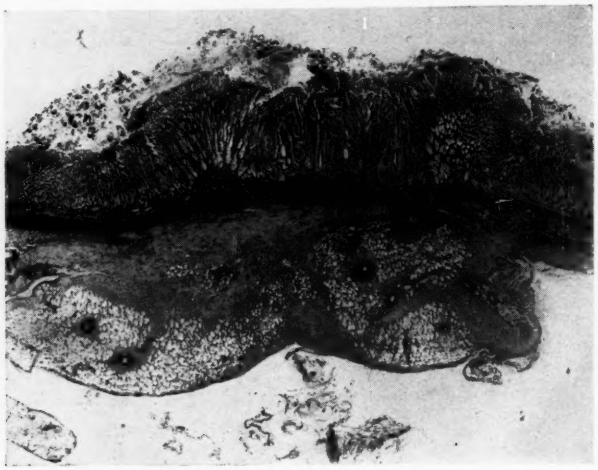


FIG. 265.—From the abdominal scars of guinea-pigs killed 21 days after operation. (× 60.) (Stain, hæmatoxylin and van Gieson.) A, Control animal; B, Sub-scurvy animal.
A, Homogenous, vascular scar composed of mature fibrocytes in a matrix of collagen; B, Extremely cellular scar composed of fibroblasts in a matrix of precollagen. (The edge of an effusion shows top left in B.) *See Fig.* 263.

incision of an animal which had been maintained in the sub-scurvy state for 20 days after operation and then allowed to develop full scurvy, dying on the thirty-fifth post-operative day. The original intermuscular septa can be seen passing right through the scar without being incorporated in it. There had been only partial removal of damaged muscle.

Examination of the sections of this series of animals also suggested that a deficiency of ascorbic acid delayed the removal of catgut ligatures, either by phagocytosis or extrusion. In the controls, the catgut of the gastrotomy wounds had disappeared by the seventeenth day. By the twenty-first day the scar was uniform and mature, with the epithelium well healed, so that the only evidence of where the incision had been was the fusion of the layers of the muscularis and substitution of the muscle by fibrous tissue. In the sub-scurvy animals the catgut ligatures remained and the incision was only partially healed (*Fig.* 266).



A

B

FIG. 266.—Cross-sections of the gastric incisions of guinea-pigs killed 21 days after operation. (× 13·5.) (Stain, silver impregnation.) A, Control animal; B, Sub-scurvy animal.
A, Uniform, neat healing; B, Irregular, delayed healing with a catgut ligature still not absorbed or extruded, and precollagen forming the intercellular substance in the subserous part of the scar.

Effects of Scurvy on Healed Wounds.—Three animals were observed for the effects of established scurvy on healed wounds. Two sub-scurvy and one control guinea-pig were deprived of all ascorbic acid from the twentieth day after operation and lived for a further 15, 19, and 25 days respectively. The first animal to die ruptured spontaneously the superficial parts of its abdominal incision on the day before death (*Fig.* 267). There was no evidence of infection. The 'scars' of this and the second animal to die, which was also from the sub-scurvy group, showed in an extreme form all the appearances already described for the partially deficient animals, except that in the centre of groups of fibroblasts the intercellular matrix was entirely structureless (*Fig.* 268). The last animal (20 days saturated with the vitamin and then 25 days without it) still showed a perfectly healed wound

at death. The new collagen of the scar had, however, reverted to an argyrophil precollagenous state (*Fig.* 269) very different from the comparable intercellular material in the scar of the control animal that had been killed on the twenty-first post-operative day. The cells of the scar appeared to be mature fibrocytes (cf. *Fig.* 263).

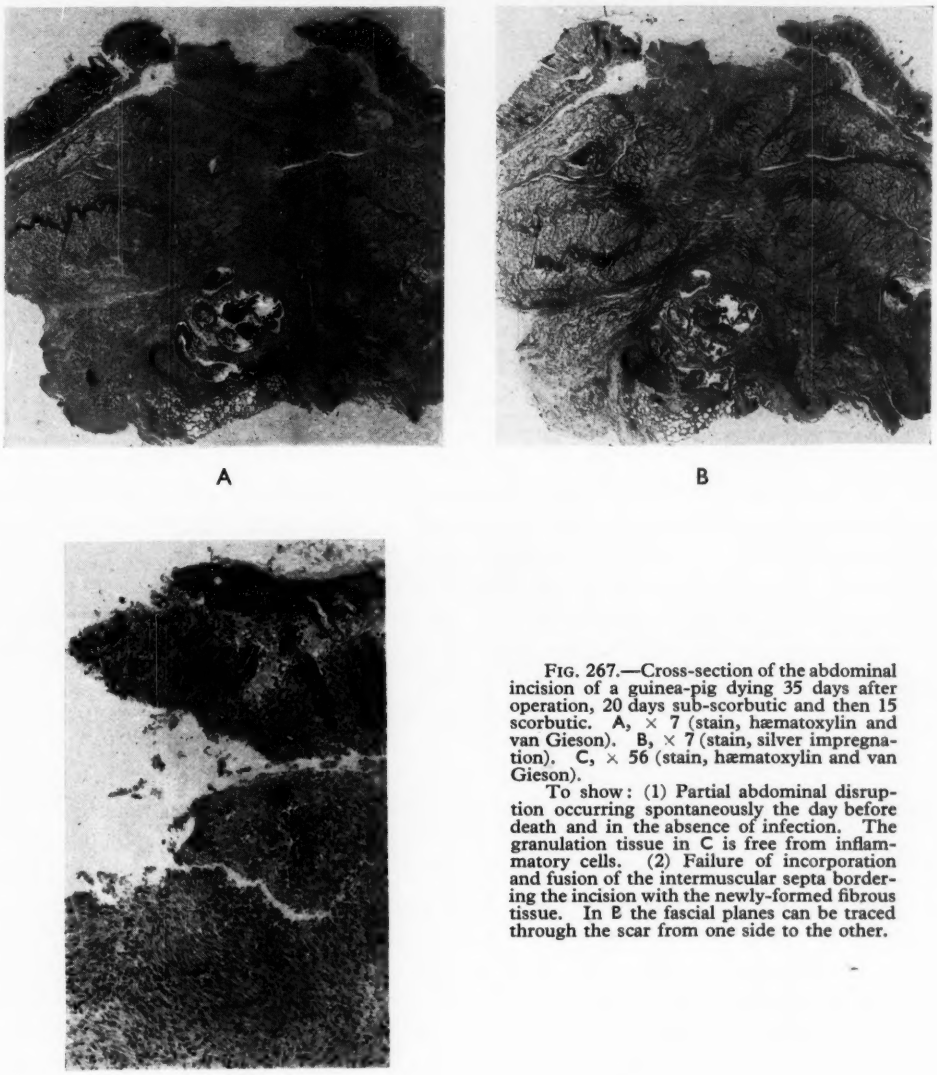
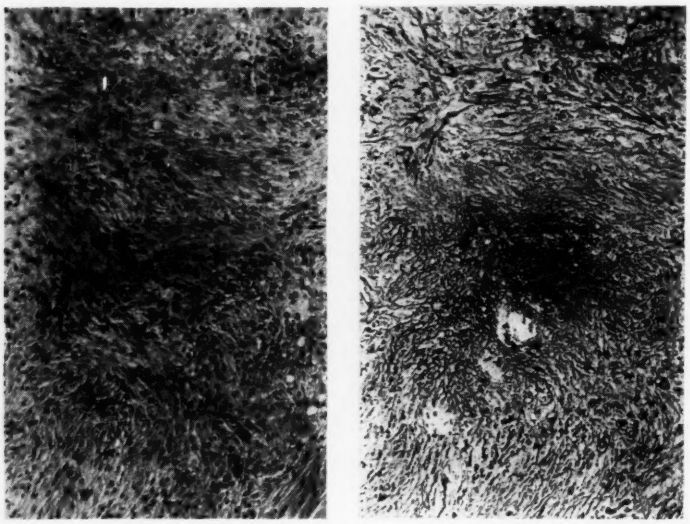


FIG. 267.—Cross-section of the abdominal incision of a guinea-pig dying 35 days after operation, 20 days sub-scorbutic and then 15 scorbutic. A, × 7 (stain, hæmatoxylin and van Gieson). B, × 7 (stain, silver impregnation). C, × 56 (stain, hæmatoxylin and van Gieson).

To show: (1) Partial abdominal disruption occurring spontaneously the day before death and in the absence of infection. The granulation tissue in C is free from inflammatory cells. (2) Failure of incorporation and fusion of the intermuscular septa bordering the incision with the newly-formed fibrous tissue. In B the fascial planes can be traced through the scar from one side to the other.

Assessing the Degree of Vitamin-C Deficiency.—The two most efficient methods of determining vitamin-C deficiency in man are the excretion of a test dose of ascorbic acid and the estimation of the ascorbic acid content of the blood. In guinea-pigs the former is impossible, and enough blood for the latter test is obtainable only by exsanguinating the animal at death. There is, therefore, no accurate standard of deficiency for comparison with human cases. The guinea-pig is known



A B

FIG. 268.—From the scar of the same scorbutic guinea-pig as *Fig.* 267. (× 88.) (Stain, A, hæmatoxylin and van Gieson; B, silver impregnation.) Consecutive sections, identical fields. To show fibroblasts with amorphous intercellular substance centrally and precollagen peripherally.

to be far more susceptible to scurvy than man, and therefore presumptive evidence, based on histological appearances, is not strictly valid: but it must be assumed, and with some degree of conviction since the histological changes in human and guinea-pig scurvy are identical, that the results of experiments on guinea-pigs are, to a considerable extent, applicable to human beings.

The following methods were used in the present experiments to assess the degree of deficiency or to exclude the presence of frank scurvy.

1. *Clinical Evidence.*—The sub-scurvy animals remained active, continued to consume a normal quantity of food, their gums and teeth remained healthy, and they had no hæmorrhages. They did not lose weight, in contrast to scorbutic guinea-pigs which were found to lose between one-third and one-quarter of their body-weight during the days preceding death (Graph, *Fig.* 270). (Höjer[21] found a comparable weight loss in a large number of scorbutic guinea-pigs.) Compared with the normal controls, on the other hand, their coats were not as shiny, they did not withstand operation so well, nor did they react to surprising external stimuli with quite the same alacrity. Hæmoglobin estimations and red blood-cell counts done on all guinea-pigs at operation and at death showed no appreciable difference between the two groups, and erythrocyte sedimentation-rates were similar in each case.

2. *Rotter's Intradermal Dye Test.*[35]—This revealed no relevant deficiency in the sub-scurvy group of animals. As a test it proved of no value, and as applied to human beings it is, in my opinion, of less value than a few questions about habits of diet.

3. *Szent-Györgyi's Test.*[38]—This gives a rough estimate of the reducing substances, particularly ascorbic acid, present in the suprarenals. Coarse sections of the suprarenal glands are cut as soon after death as possible (immediately in the case of the animal experiments), cleaned of blood and serum with blotting paper, and placed in 0·4 per cent neutral silver nitrate solution in the dark for 15 minutes.

The degree of reduction of the silver nitrate, shown by the blackening of the tissue, indicates the amount of reducing substance present in the tissues. The control group, according to this test, contained about three times as much ascorbic acid in

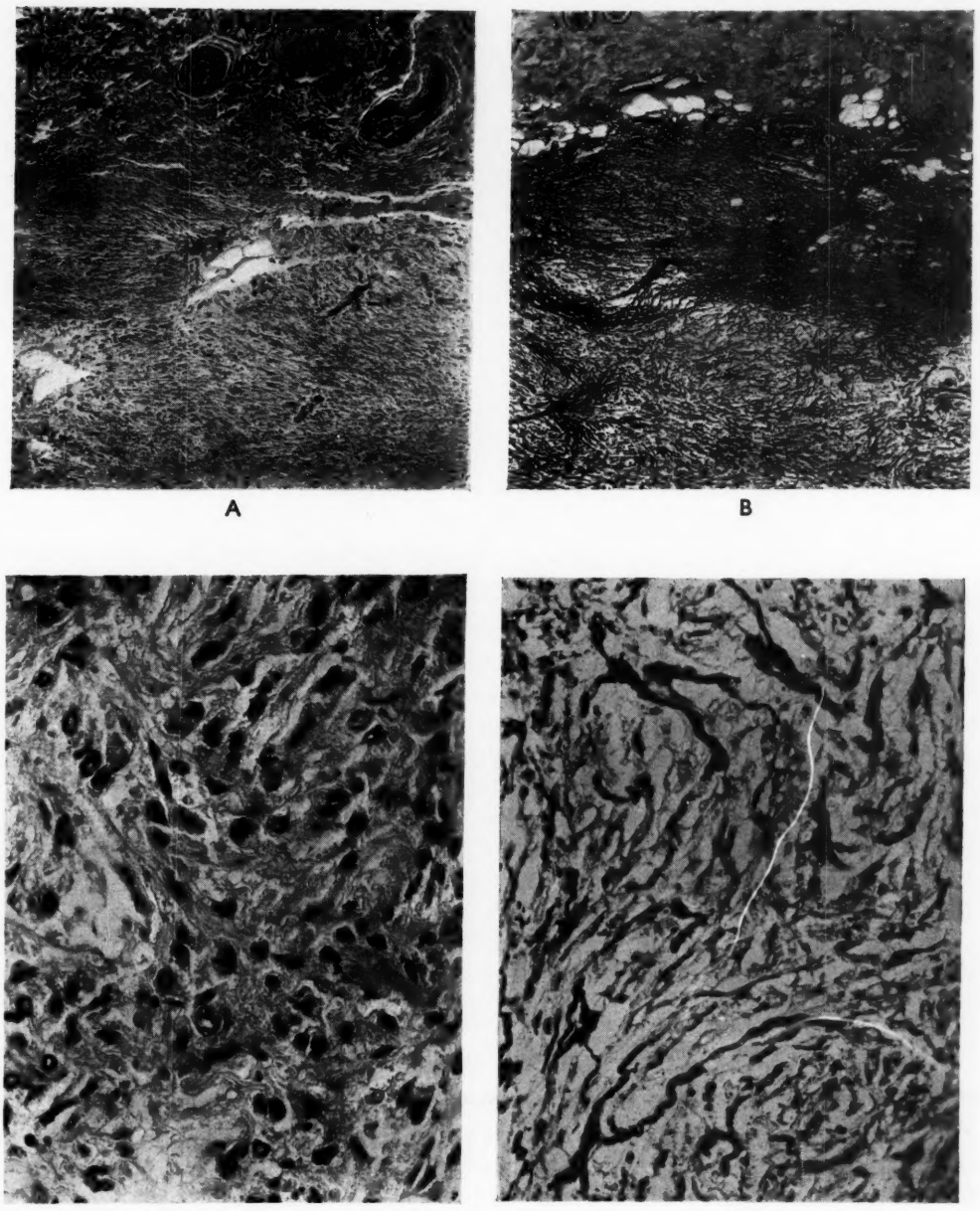


FIG. 269.—From the abdominal scar of a guinea-pig dying 45 days after operation, 20 days normal and then 25 scorbutic. A, × 56 (stain, hæmatoxylin and van Gieson); B, × 56 (stain, silver impregnation); C, × 400 (stain, hæmatoxylin and van Gieson); D, × 400 (stain, silver impregnation).

To show: (1) Reversion of newly-formed collagen to precollagen (B and D). Compare the wound of this animal, which healed normally for 20 days, with that illustrated in *Fig.* 263, A, 21 days of normal healing. (2) Fibrocytes in the scar (C), cf. *Fig.* 263, B. (3) Collagen remaining in the established fibrous tissue of the corium (A and B).

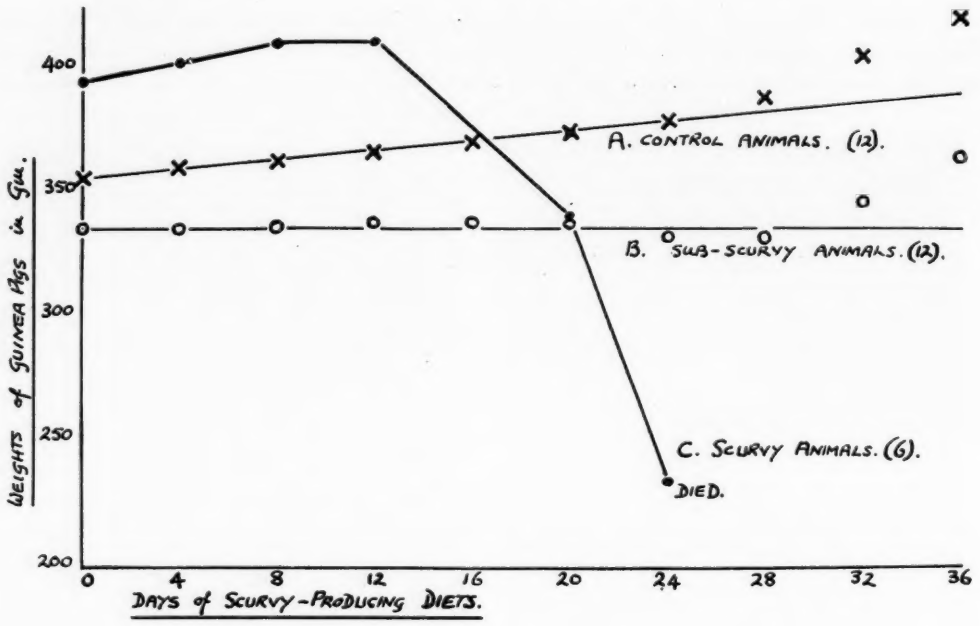


FIG. 270.—Graph showing the average weights of three groups of guinea-pigs.

their tissues as the sub-scurvy animals, yet all of the latter contained an appreciable amount. Scorbutic guinea-pigs were shown to contain none.

4. *Microscopical Evidence.*—Microscopical sections were made of the hearts, suprarenals, and costochondral junctions of all the guinea-pigs. The hearts and suprarenals of the sub-scurvy animals showed none of the degenerative changes found in scurvy,[20, 21] but the costochondral junctions showed changes intermediate between the normal and scorbutic (*Fig.* 271).

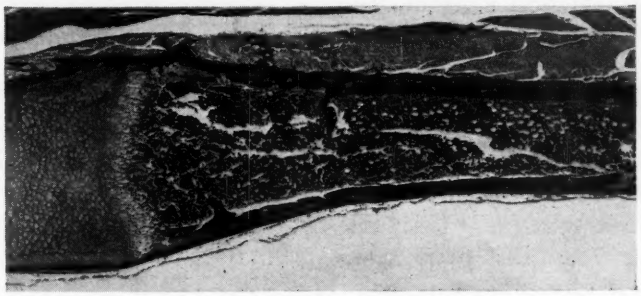
5. *Blood Estimations.*—Blood ascorbic acid estimations on 3 animals from each group showed an average of 0·46 mg. per 100 c.c. for the controls and 0·35 mg. for the sub-scurvy animals. These estimations are too few in number, yet the readings for the animals of each group were surprisingly constant.

Taking all the tests into consideration, it is evident that a state of severe deficiency was induced in the sub-scurvy animals, bordering, but not trespassing, on scorbutus major.

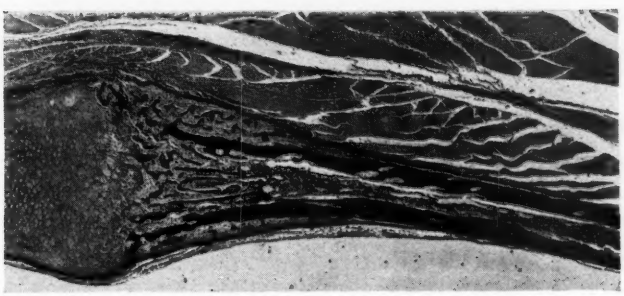
B. HUMAN EXPERIMENT

The subject of the experiment, a young adult male in the best of health, ate no fruit, preserves, jam, or uncooked vegetables, and consumed only one portion of cooked vegetable each day for 3 months. By this time the blood ascorbic acid content, estimated seven times, averaged 0·34 mg. per 100 c.c. Under local anæsthesia a left submammary incision 1½ in. long was made down to muscle. It was closed with a continuous 0 chromic catgut suture for the pectoral fascia and interrupted silk stitches for the skin. At the end of two weeks this incision was excised and a second identical incision made on the opposite side. 1000 mg. of ascorbic acid were then taken by mouth in divided doses for three days and then 400 mg.

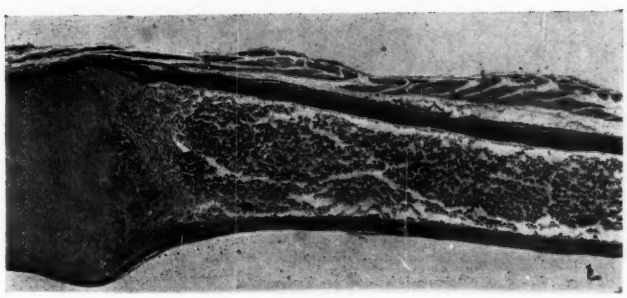
daily till the end of the second fortnight, when the second wound was excised. The blood ascorbic acid rose to 0·5 mg. in three days and remained at that level. Twelve days after the second incision, a test dose of 400 mg. of ascorbic acid taken by mouth



A



B



C

FIG. 271.—Costochondral junctions of growing guinea-pigs. (× 16.) (Stain, hæmatoxylin and van Gieson.) A, Control animal. B, Sub-scurvy; C, Scurvy.
Note: (1) In B, increase of cellular activity and calcification of cartilage columns. Cortex of good thickness and staining power. (2) In C, cessation of all calcification or ossification. Cortex thin and poorly staining. The 'framework marrow' (Gerüstmark) of proliferating mesodermal cells replaces the red bone-marrow near the cartilage.

showed a 61 per cent excretion in 6 hours, indicating a high degree of saturation. Both incisions were treated for histological examination in the same way as the guinea-pig scars. Both healed perfectly, with no macroscopical or microscopical difference and with identical reactions to the catgut ligature.

C. HUMAN NECROPSY MATERIAL (*Table I*)

Abdominal incisions, gastro-intestinal anastomoses and stomata, sutured duodenal ulcers, one repaired intestinal rupture, and some other specimens were obtained from an unselected consecutive series of 28 relevant cases. Each specimen was prepared for histological examination by the same methods as those used in the guinea-pig experiments. The routine administration of vitamin for all such cases had not been recognized so that some cases had received ascorbic acid and some had not. Blood ascorbic acid estimations were seldom available. Szent-Györgyi's test[38] was done in 17 cases as set out in *Table I*. The outbreak of war prevented the accumulation of a more complete series, but it was decided, as a result of a careful histological study of the material so far available, to place on record the findings in this present small selection. (Biopsies of healing wounds and granulation tissue taken during life were found to be too fragmentary to be of any value.)

Analysis of the Post-mortem Findings.—*Table I* is self-explanatory in placing certain aspects of wound healing side by side with the histological appearances of the wounds, the amount of supplementary ascorbic acid given, and, in 17 of the cases, a rough estimate of the ascorbic acid content of the tissues. Wound infection was common in certain groups of cases, particularly the perforated peptic ulcers,

Table I.—SUMMARY OF

CASE NO.	SURVIVAL AFTER OPERATION	NATURE OF DISEASE	NATURE OF OPERATION	CAUSE OF DEATH
1	Days 1	Acute gastric ulcer; hæmatemesis	Gastro-enterostomy	Heart failure
2	2	Carcinoma of stomach	Gastro-enterostomy and entero-enterostomy	Heart failure
3	2	Carcinoma of pancreas	Cholecyst-gastrostomy	Liver shock
4	3	Perforated duodenal ulcer	Suture with drainage	Diffuse peritonitis
5	3	Perforated duodenal ulcer	Suture without drainage	Diffuse peritonitis with *B. welchii* septicæmia
6	4	Gastric ulcer-cancer	Partial gastrectomy	Diffuse peritonitis
7	4	Strangulated umbilical hernia	Relief of obstruction with resection and anastomosis	Diffuse peritonitis
8	5	Chronic gastric ulcer	Partial gastrectomy	Diffuse peritonitis
9	6	Carcinoma of cardia	Œsophagogastrostomy	Diffuse peritonitis; pericarditis; pyelonephritis
10	7	Perforated duodenal ulcer; carcinoma of bladder	Suture without drainage	Bronchopneumonia
11	8	Carcinoma of stomach	Partial gastrectomy	Bronchopneumonia; subphrenic abscess

but it interfered with healing to the extent of causing a breakdown of the wound in 1 case only, *Case* 23. Infected sinuses are not included under abdominal disruptions. Complete disruption implies a rupture of all the layers of the abdominal wall, not necessarily extending for the whole length of the incision. Some of the cases which died during the first few days after the operation showed no ' reaction ' at the suture line. This proved on microscopical examination to be due to necrosis or failure of cellular proliferation or a combination of these two factors.

It has been shown that collagen, in normally healing wounds, becomes evident at the end of the first week and then steadily increases in amount. Of the 18 cases dying after the seventh day, eight (*Cases* 11, 13, 14, 15, 17, 22, 25, and 27) showed precollagen in place of collagen. In all these cases there was good indication that there had in the past been an insufficient intake of vitamin C. Only 1 had received supplementary ascorbic acid and that in inadequate doses (*Case* 25). In 4 cases (*Cases* 11, 13, 17, and 27) the Szent-Györgyi test indicated negligible amounts of ascorbic acid in the tissues, in 3 (*Cases* 14, 22, and 25) small amounts, and in *Case* 15 the test had not been done. This small group of 8 cases included all 5 in which abdominal disruption had occurred in the absence of gross infection. Three had also leaked at the suture line without local necrosis. Microscopically their wounds were

28 HUMAN CASES

ABDOMINAL DISRUPTION	LEAKAGE AT SUTURE LINE	NECROSIS AT SUTURE LINE	CELLULAR PROLIFERATION	INTERCELLULAR SUBSTANCE FORMATION	ASCORBIC ACID GIVEN	SZENT-GYÖRGYI TEST
No	No	Superficial	None	None	1000 mg.	$\frac{1}{3}$
No	No	No	None	None	0	$\frac{2}{3}$
No	No	Marked	Beginning	None	0	$\frac{1}{2}$ (0·4 mg. ascorbic acid /100 c.c. blood)
No	No	No	Present	None	0	$\frac{2}{3}$
No	No	No	Present	None	0	$\frac{2}{3}$
No	No, but incipient	Complete	Present	None	6200 mg.	—
No	Yes	Yes	Marked	Precollagen	0	$\frac{2}{3}$
No	No	No	Present	None	Inadequate doses	—
No	Yes	Complete	None	None	0	—
No	No	No	Moderate	Precollagen	0	—
Partial	Yes	No	Present	A little precollagen	0	0

Table I.—SUMMARY OF

CASE NO.	SURVIVAL AFTER OPERATION	NATURE OF DISEASE	NATURE OF OPERATION	CAUSE OF DEATH
12	Days 8	Duodenal ulcer with pyloric stenosis	Gastro-enterostomy	Heart failure; dilatation of stomach
13	8	Carcinoma of cardia	Witzel jejunostomy	Diffuse peritonitis; bronchopneumonia
14	12	Carcinoma of ampulla of Vater	Cholecystgastrostomy	Pyelonephritis; suppurative parotitis
15	12	Chronic gastric ulcer	1. Partial gastrectomy 2. Abdominal suture	Diffuse peritonitis
16	12	Perforated duodenal ulcer	Suture without drainage	Diffuse peritonitis; bronchopneumonia
17	13	Traumatic rupture of jejunum	1. Suture with drainage 2. Re-drainage	Diffuse peritonitis with abscesses
18	17	Gastric ulcer with hæmatemesis	1. Excision of ulcer 2. Gastro-enterostomy	Hypostatic pneumonia
19	17	Carcinoma of colon	Resection and anastomosis	Diffuse peritonitis
20	18	Duodenal ulcer with hæmatemesis	Partial gastrectomy	Agranulocytosis
21	20	Subacute gastric ulcers; hæmatemesis	Exploratory laparotomy	Bronchopneumonia; pyæmia
22	22	Carcinoma of rectum	1. Colostomy 2. Perineo-abdominal excision	Diffuse peritonitis
23	22	Perforated duodenal ulcer with pyloric stenosis	Suture and gastro-enterostomy without drainage	Tuberculous bronchopneumonia
24	23	Jejunal ulcer (10 years gastro-enterostomy)	Partial gastrectomy and entero-enterostomy	Diffuse peritonitis and empyema
25	28	Perforated duodenal ulcer	1. Suture with drainage 2. Drainage of subphrenic abscess	Subphrenic abscess and empyema
26	39	Intestinal obstruction from abdominal metastases of bronchial carcinoma	Gastro-enterostomy and entero-enterostomy	Multiple metastases
27	39	Perforated duodenal ulcer	1. Closure without drainage 2. Drainage of subhepatic abscess	Subphrenic and subhepatic abscesses
28	Years	Multiple injuries	Old healed gastro-enterostomy	Multiple injuries

28] HUMAN CASES—*continued*

ABDOMINAL DISRUPTION	LEAKAGE AT SUTURE LINE	NECROSIS AT SUTURE LINE	CELLULAR PROLIFERATION	INTERCELLULAR SUBSTANCE FORMATION	ASCORBIC ACID GIVEN	SZENT-GYORGYI TEST
No	No	Superficial	Marked	Precollagen and collagen	1800 mg.	½
Partial	No	No	Scanty	A little precollagen	0	Trace only
No	No	No	Present	Precollagen	0	½
Complete. 10th day, resutured	Yes	No	Marked	Scanty, precollagen only	0	—
No	No	No	Good	Good, mostly collagen	2600 mg.	Saturation
Complete	Yes	No	Good	Precollagen, with little collagen	0	Trace
Gastric fistula	At fistula only	No	Good	Collagen	100 mg. daily for 40 days	⅔
No	No	No	Good	Collagen	0	—
No	No	No	Good	Collagen	0	⅔
No	—	—	(Skin only) Poor	Collagen	6600 mg.	½
No (sloughing perineum)	No	No	Adequate	Collagen and precollagen	0	½
Complete. Transverse incision	No (omental closure)	No	Good	Collagen at gastroenterostomy, precollagen at abdominal wall	5000 mg.	⅔
No	No	No	Good	Collagen	0	—
Partial	No (omental closure)	No	Scanty	Precollagen	Inadequate dose for last few days	½
No	No	No	Good	Collagen	800 mg.	—
No	No (omental closure)	No	Poor	Precollagen	0	Trace
Healed anastomosis for comparison with other cases						

very similar to those of the sub-scurvy guinea-pigs. *Fig.* 273 shows the skin incision of *Case* 17, who died 13 days after operation. The corium is opened out internally and the gap is filled by proliferating fibroblasts producing precollagen. For comparison, *Fig.* 272 illustrates a similar wound in *Case* 16, who died 12 days after operation, but who had received plenty of vitamin C. Abdominal distension had been similar in the two cases.

ILLUSTRATIVE CASE RECORDS

Case 16.—W. H., male, aged 50. Admitted July 8, 1939, with a perforated duodenal ulcer. Operation for closure, without drainage of the peritoneal cavity, was done eight hours after the perforation had occurred. Peritonitis developed, with vomiting and abdominal distension from ileus. Treatment with morphia and intravenous fluids was begun immediately. The hæmoglobin remained at 80 per cent. On July 14 the patient developed bronchopneumonia which was treated with sulphapyridine. From July 16 onwards, ascorbic acid was also given, totalling 2600 mg. in divided doses, either by mouth or intravenously. On July 18, venesection of 800 c.c. of blood was done for left-sided heart failure, but the patient died on July 20, twelve days after operation.

Necropsy was done on July 21. The heart failure was evident and the lungs showed a diffuse *B. Pfeiffer* bronchopneumonia. The abdomen was distended, but the midline incision was well healed in accurate approximation. The peritoneum showed a diffuse purulent peritonitis (mixed infection) with, in addition, a small localized abscess around the duodenal ulcer. There was no leak through from the lumen. The Szent-Györgyi test indicated a saturation of the tissues with ascorbic acid and the histological findings agreed with this estimate.

Sections of the skin showed that the corium had healed in exact apposition without any reduction in thickness and with good collagen formation, which was almost indistinguishable in the van-Gieson-stained section from the adjacent established fibrous tissue. Silver impregnation showed little remaining precollagen (*Fig.* 272). The ulcer showed no sign of epithelial healing, but the perforation was well closed. There was great mesodermal proliferation with the formation of collagen as well as precollagen in the actual floor of the ulcer. (Usually the intercellular substance of granulation tissue exposed to an infected space is entirely precollagenous in nature, whether that space is an abscess or the internal or external surface of the body.)

Case 17.—J. B., an under-nourished boy of poor physique, aged 17. Admitted July 14, 1938, in a state of severe shock, having been crushed between two motor cars. On recovery

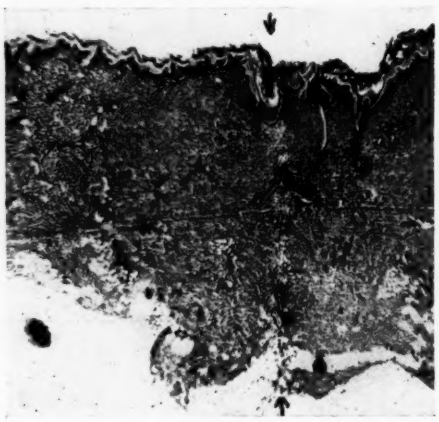


FIG. 272.—Cross-section of the sutured skin incision in *Case* 16. (×16.) (Stain, silver impregnation.) There is exact apposition of the cut edges. Little precollagen remains. (Cf. *Fig.* 273.)

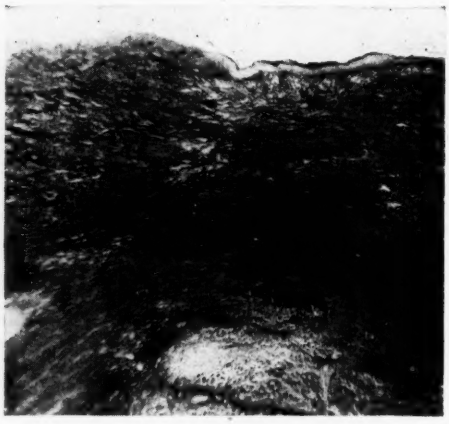


FIG. 273.—Cross-section of the sutured skin incision in *Case* 17. (× 16.) (Stain, silver impregnation.) The opposed edges of the corium are stretched apart and the gap filled by immature precollagenous scar. (Cf. *Fig.* 272.)

from the shock it became evident that a viscus had been ruptured. The abdomen was explored through a right paramedian incision and a circumferential tear, 2 in. long, was found on the antimesenteric border of the jejunum 6 in. from the duodenojejunal flexure. It was closed with thread sutures and oversown. The peritoneum was drained through a separate suprapubic stab incision. The peritoneal fluid grew both aerobic and anaerobic organisms, but the patient made good progress. Intravenous therapy was continued till July 19, and on July 22 the stitches were removed. The wound was partially infected and gradually gaped open, although the abdomen was only moderately distended. On July 27, 12½ days after the accident, there was sudden severe abdominal pain, more on the left side than on the right, suggestive of perforation of a viscus. A second drainage of the peritoneum was done through a left muscle-splitting incision. The patient died on July 28, 13 days after the first operation.

Necropsy was done on the same day within a few hours of death. The abdomen was moderately distended and the incision was gaping open for some of its length, with loops of adherent small intestine effectively closing the gap. At either end the incision was stretched without separation of the edges and without macroscopical infection. The peritoneum showed diffuse plastic peritonitis of recent origin, with localized abscesses of longer standing. The suture line itself formed a linear ulcer 1 cm. in width, traversed by thread sutures lying partly free in the lumen of the jejunum, with a perforation 1 mm. across communicating with the general peritoneal cavity.

The boy had been given no vitamin C and had received nothing but intravenous fluids for most of the time he had been in hospital. The Szent-Györgyi test indicated a mere trace of vitamin C in the tissues.

Microscopically the skin incision, where best healed, showed complete epithelialization, but the opposed surfaces of the corium were stretched apart and the gap filled, under the new epithelium, by a mass of proliferating fibroblasts producing precollagen only (*Fig.* 273). Deeper, this granulation tissue was very vascular and was producing small quantities of immature collagen as well as precollagen. There was no pus formation and but little infiltration by mononuclear cells. In other regions where the scar was even more stretched, the gap was filled by nothing more than loose-textured œdematous granulation tissue in which there was little precollagen and no collagen.

The intestinal suture line, from lumen to serosa, consisted of similar unhealthy granulation tissue broken up by collections of œdema fluid and microscopical abscesses. In no place was the healing satisfactory, except from the point of view of cellular proliferation, and it gave the appearance of imminent breakdown along its whole length. The picture, both in the abdominal incision and intestinal suture line, reproduced almost exactly the appearances in the sub-scurvy group of guinea-pigs.

DISCUSSION AND CONCLUSIONS

It has been shown experimentally on guinea-pigs that a partial deficiency of vitamin C produces a most profound disturbance in the healing of clean wounds. When there is sufficiency of the vitamin, the mesodermal cells build up a mature vascular scar, composed of fibrocytes, collagen, and small blood-vessels, within 14 days. In scurvy the only intercellular material produced is fluid and amorphous. In the intermediate state of sub-scurvy, when the deficiency is severe though not clinically evident, the scar matrix remains immature and of poor holding power, though it is produced in adequate amounts. (Cf. the two graphs, *Figs.* 261, 262.) The divergence between the tensile strength of the healing wound and the cellular proliferation becomes most marked on about the tenth day after operation, the time when wound disruption is commonest. The quantitive relationship between the vitamin-C content of the tissues and the maturation of the intercellular substance has not been worked out. It is not known whether a state of saturation is necessary for the most rapid and effective deposition of collagen, or whether a vitamin content far short of saturation is enough.

As a concomitant of this defect in collagen production the whole architecture of the healing wound is disturbed. The proliferation of fibroblasts, at first apparently normal in rate, continues so long as the scar production is abnormally retarded. The cells remain immature. Blood-vessels do not readily penetrate this ill-formed granulation tissue. Hæmatomata are not organized or absorbed, and the scar becomes split up by further extravasations of blood-stained œdema fluid. The phagocytosis of damaged tissues is delayed and the supporting structures bordering upon the incision are not satisfactorily incorporated in the newly-formed scar. These secondary effects may well be due to a disturbance of the blood-supply or vascular permeability, but this is itself directly or indirectly due to the deficiency of vitamin C. It is further suggested that the absorption of catgut ligatures may be delayed.

When scurvy supervenes on a recently healed wound, the newly-formed collagen of the scar has been shown to revert to precollagen. Yet the established fibrous tissue bordering the incision, from which the recently laid down scar is barely distinguishable before the advent of scurvy, does not revert in this manner (*Fig.* 269). This indicates that our present methods of demonstration are inadequate to show the finer differences between the various states of white-fibrous-tissue fibres and that scars do not fully mature for many months at least. The ready reversion of the collagen of scars to its immature and weaker form offers an explanation of the breaking down of healed wounds in scurvy (*Fig.* 269).

Studies of human wounds are of necessity less well controlled and lead to less definite conclusions than animal experiments. It should be remembered that when attention is focused on one aspect of the problem, greater care is bestowed on all the other factors concerned. It is, therefore, of no scientific value to state that wound disruption has been reduced by about 75 per cent since the routine administration of ascorbic acid has been adopted for all major abdominal operations. This, however, has been the case, and leakage from suture lines has occurred in but one of a large number of operations during the past 30 months. When wounds have thus failed to heal in spite of adequate supply of the vitamin, there always was gross local infection, with or without a hæmatoma, or ischæmic necrosis. This emphasizes the importance of ordinary studied operative technique and meticulous post-operative care. The mechanical strains of coughing and vomiting and of abdominal distension must be minimized until the wound is fully healed.

In the 28 human cases which were studied post mortem, 10 died within the first week when collagen production is not to be expected. Of the remaining 18, those most deficient in vitamin C showed poorest collagen production. In 5, the failure to form scar tissue was a contributary cause of death, by facilitating the breakdown of the abdominal wound, leakage from the suture line, or both. In 4 of these 5 cases the disruption occurred between the eighth and thirteenth days. It is significant that wounds most commonly break down on about the tenth day, and it is possible that, by saturating all patients with vitamin C, this major bloc of wound disruptions may be eliminated. Leaks and disruptions due to other causes were found to occur earlier or later than this. However, the cases are not numerous enough and the control of the vitamin-C content of the tissues not accurate enough for definite conclusions to be reached on this evidence alone. Taken in conjunction with the animal experiments, the results are presented as being very suggestive that a partial deficiency of vitamin C produces effects which are as important in the healing of human wounds as in those of guinea-pigs.

The human experiment showed that there was no difference between wounds made before and after the administration of ascorbic acid. Crandon and Lund[9] induced a marked deficiency in a healthy human subject in only three months and showed that a wound healed well. Isolated observations such as these suggest that the critical level for vitamin C in the formation of collagen is probably well below saturation point, though they should not be regarded as conclusive. Short-lived deprivation in an otherwise healthy individual does not compare with patients suffering from chronic illnesses with long-standing deficiencies.

The relationship between local infective processes and vitamin-C concentration has, unfortunately, not been investigated histologically. By analogy with the clean-wound healing experiments, it is reasonable to presume that all subacute and chronic infective lesions would be assisted in their healing by saturation with the vitamin. Evidence to support this contention from the clinical standpoint is to be found as far back as 1924, when Höjer[21] noted that the progress of cases of pulmonary tuberculosis was materially improved by the addition of one orange daily to the diet. Healing, after all, is a single process, whatever the tissue and whether infection is present or not. All patients, therefore, who suffer from localized chronic infective diseases, particularly tuberculosis and residual osteomyelitis, are advised to modify their diets, if they are not already satisfactory, so as to consume more fruit and vegetables and to cook these foods so as to conserve as much of the vitamin as possible. This change in diet should be permanent.

It is not the purpose of this paper to discuss wound healing apart from its relationship with vitamin C, but it is thought advisable that other factors should be briefly mentioned.

Hypoproteinaemia and the Administration of Parenteral Fluids.—Poor cellular proliferation occurs commonly, and was found in 5 out of the 28 human cases studied histologically. Epithelium and mesothelium are both concerned, so that the separated edges of the wound (even if it has broken open as late as in the third week) may appear as if the incision had just been made. Hypoproteinæmia is partly responsible for this lack of cellular response.

In such cases it is of little avail to saturate with vitamin if the lack of protein is not also attended to. When fluids are being administered entirely by the rectal or intravenous routes, there is a tendency to give blood only when the hæmoglobin falls below a certain arbitrary level. Such cases may not be deficient before operation, but may develop hypoproteinæmia after the intravenous therapy has begun and in the absence of anæmia. The blood-proteins should, therefore, be repeatedly estimated and maintained.

Œdema consequent on protein deficiency is of particular importance at gastric and intestinal anastomoses where trauma and infection already predispose to an inflammatory œdema. To aggravate the condition further will certainly interfere with the healing.

Ligature Material.—Ligature material also affects the appearance of wounds, though no instance suggestive of catgut sensitivity[25, 33] has been seen.

Local Applications.—The bombing of London has unfortunately provided opportunities for testing out the efficacy and effects of the sulphonamides in potentially infected wounds. The powder, sprinkled into the excised wound, indubitably delays healing. The experimental work of Bricker and Graham[6] supports this finding, whereas Mayo and Miller[30] consider that a saturated solution of sulphanilamide in normal saline stimulates healing.

Administration of Vitamin C Before and After Operation.—1000 mg. of ascorbic acid, given daily for three days, is enough to produce saturation even in a grossly deficient patient, and 100 mg. daily to maintain it. These doses are increased in cases of infection, new growth, chronic gastro-intestinal disease, and achlorhydria. The daily dose should be divided so as to minimize the rapid excretion due to the low renal threshold. It should be combined with dilute hydrochloric acid when achlorhydria is present or suspected, as in carcinoma of the stomach and ulcerative colitis. It should be given intravenously or intramuscularly when circumstances are such that it cannot be given by mouth. In intravenous drip infusions, a maximum of 200 mg. of sodium ascorbate ('redoxon') is added to each pint. The saline should have been recently heat-sterilized to drive off the contained air. Ascorbic acid itself is more easily destroyed and is more irritating to the intima of the vein than the sodium salt. Both these substances produce considerable local irritation when given by intramuscular injection, but it has been suggested that the mono-ethanolamine salt can be given safely and effectively by this route without producing any immediate or delayed systemic or local reaction.[28]

The normal intake of vitamin C should be 50 mg. daily, though this will not produce saturation of the tissues. Few of the poorer classes of this country consume more than a fraction of this amount and yet the majority remain in the best of health. However, a good physique and a ruddy complexion is no criterion of the healing power of the tissues. Vitamin C has been shown to be of the greatest importance in wound healing, though it is not a panacea. The present paper has stressed its value particularly in the healing of soft-tissue scars, but it is of equal value in the laying down of other intercellular substances such as bone. It should be administered: (1) when clean and quick healing of the wound is particularly desirable, (2) in major abdominal operations, (3) when a hollow viscus has been opened, (4) when post-operative complications are anticipated, (5) where there is evidence of a nutritional deficiency, and (6) in all cases of serious injury. On the evidence at present available, these patients should be saturated, if possible before operation. In emergencies, saturation point should be reached before the seventh day.

SUMMARY

1. Collagen does not form in the healing wounds of guinea-pigs partially deficient in vitamin C. The intercellular substance remains immature and of poor holding power.

2. The proliferating mesodermal cells also fail to mature.

3. The healing of the wound as a whole is profoundly disturbed in this experimental sub-scurvy.

4. The collagen of normally healed wounds reverts to precollagen if scurvy supervenes.

5. A series of 28 human cases were studied post mortem. In 8 the wounds showed a deficiency in the formation of collagen resembling that in the sub-scurvy guinea-pigs.

6. In these 8 cases, there were 5 instances of abdominal disruption and 3 of leakage at gastro-intestinal suture lines.

7. Vitamin C, in good concentration, is of the greatest importance in wound healing.

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CHOLESTEROSIS OF THE GALL-BLADDER
A FURTHER CONTRIBUTION TO THE HISTOLOGY OF THIS CONDITION

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CHOLESTEROSIS of the gall-bladder, appositely termed 'strawberry gall-bladder' because of the yellow stippling of the gall-bladder lining, is a condition due to infiltration of the mucous membrane with lipoid which is in large measure doubly refracting. The infiltration affects both lining epithelium and subepithelial tissue in varying degree. In the past there has been acute difference of opinion upon the nature of the mechanism involved, whether the lipoid is in process of excretion into the lumen of the gall-bladder or has been taken up from the bile. The subject was reviewed by the writer recently (1937), and it was shown that the balance of the available evidence indicates that cholesterosis of the gall-bladder is probably simply a 'visualization' of a normal process of resorption of lipoid and fat from the bile. It is unnecessary to repeat the arguments stated then, and as there has been no important subsequent contribution, the present paper may be considered as a postscript to the earlier review.

CASE REPORT

The case presented is of considerable interest. A pre-operative diagnosis of cholesterol polyp was made on radiological grounds. The histology of the excised gall-bladder, the writer believes, shows more clearly than any hitherto published material the physiological processes at work in the production of the condition.

Mrs. J. L., aged 53, under treatment for chronic rheumatism, came to the Out-patient Department of Glasgow Western Infirmary in October, 1936, complaining of vague dyspeptic symptoms, including nausea and right hypochondriac discomfort and flatulence. Her symptoms were not especially associated with the taking of food, and she had no 'selective dyspepsia'. She was moderately tender in the right hypochondrium.

Cholecystographic investigation was carried out by Dr. J. S. Fulton, who reported: "The patient has a papilloma of the gall-bladder. The lesion is situated on the antero-lateral wall of the organ some 2 in. from the fundus." (*Fig.* 274.)

The patient was admitted, and on November 3 Mr. Roy F. Young operated. The gall-bladder appeared healthy on inspection. There was some evidence of chronic pancreatitis. The gall-bladder was excised. Recovery was uninterrupted.

Dr. A. C. Lendrum reported on the gall-bladder as follows: "The gall-bladder shows a fine generalized infiltration with cholesterol (strawberry gall-bladder). Histologically the fats are contained mainly in large cells which form masses distending the subepithelial loose tissues, in two or three places forming larger pedunculated masses. One of these, the largest, corresponded radiologically (after removal and fixation in the distended state) with the original radiological finding (*Fig.* 275). Fine granules of fat are also present in the epithelium."

Because of the interest and importance of the specimen, further histological studies were made for me by Dr. T. W. Govan. Frozen sections were cut from one of the polyps and from part of the non-polypose but lipoid-infiltrated mucosa.

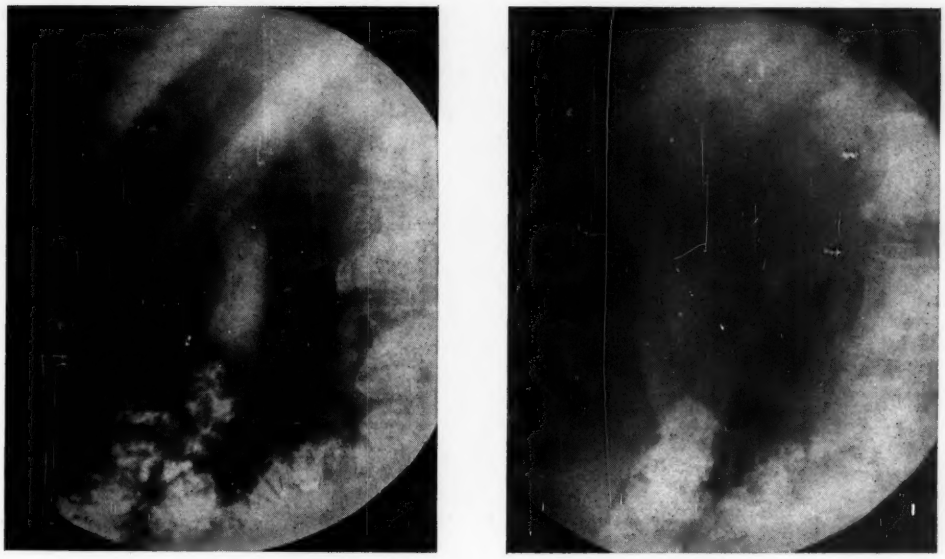

FIG. 274.—Cholesterol polyp in gall-bladder (cholecystograms). The polyp is seen as a small negative shadow close to the lateral wall of the gall-bladder. The concentrating function of the gall-bladder is well preserved, and it throws a dense shadow despite the fact that a considerable amount of dye has passed on into the colon.

FIG. 275.—Cholesterol polyp in gall-bladder (radiograph). The gall-bladder has been removed and is shown distended with air. The polyp is seen in profile, roughly triangular in shape and with a narrow base.

FIG. 276.—Cholesterosis of the gall-bladder with lipoid polyposis. This is a thin-walled gall-bladder. The outer coats consist of delicate fibrous tissue. The mucosa is pale and shows delicate stippled outlining of its plicæ with opaque bright yellow lipoid. At several points polyps have developed, one of them, that nearest the fundus, being quite large. These polyps are lobulated. (*Natural size.*)

Sections were stained with hæmatoxylin and scarlet red, with Nile-blue sulphate, and with Sudan black. These stains clearly demonstrated the lipoid nature of the infiltrate both in the subepithelial macrophages and in the epithelial cells. The polarizing microscope showed that large amounts

FIG. 277.—Section of cholesterol polyp] (low power). The section shows the general structure of a fragment of a cholesterol polyp. There is a complex pattern of glandular epithelium roughly suggestive of a papillary adenomatous formation. The stroma is fairly abundant and shows very rich lipoid deposit, although the lipoid is not uniformly distributed.

of the fat in the macrophages were in a fluid-crystalline doubly-refractile state. It was not possible to obtain doubly-refracting phenomena from the granules and globules in the epithelial cells. There were no inflammatory changes in the gall-bladder wall.

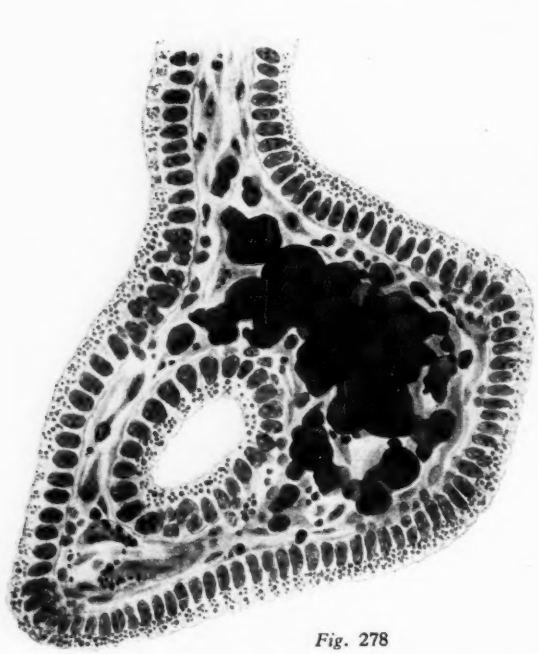

Fig. 278

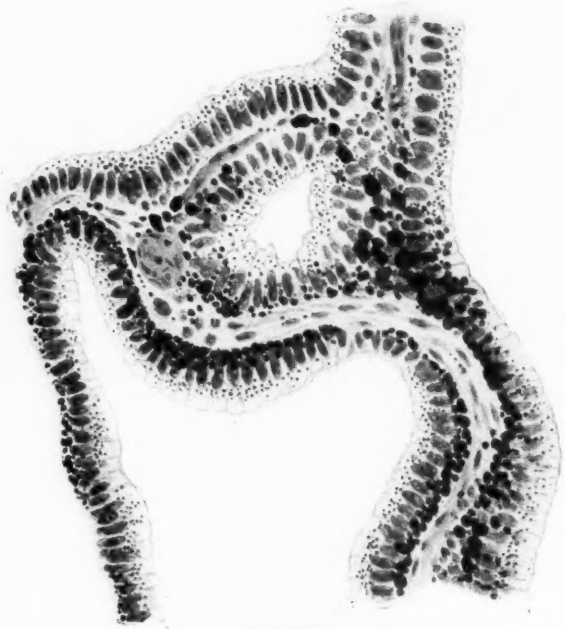

Fig. 279

FIG. 278.—Water-colour drawing of portion of cholesterol poylp, stained hæmatoxylin-Scharlach R. There is a rich deposit of lipoid (staining brightly red) principally in the connective tissue, and to a lesser extent in the mucosal epithelium. In the connective tissue all stages of lipoid storage may be seen from the appearance of a few globules in macrophage cells, indistinguishable from ordinary connective-tissue cells, to fully formed 'foam cells' enormously blown out with finely emulsified fat. In the columnar epithelium the lipoid distribution is uniform and noteworthy. Lipoid occurs in the clear portion of the columnar cells distal to the nucleus as globules and granules of various size arranged in a fairly regular gradation, with the smallest near the free border of the cell.

FIG. 279.—Water-colour drawing of richly plicated area of gall-bladder mucous membrane with abundant interepithelial lipoid. In this area of mucous membrane there is a great deal of brightly-stained lipoid to be seen distributed as granules and globules. The feature of outstanding interest is that this lipoid is confined almost entirely to the epithelial cells, although a few small stromal lipoid-filled macrophages can be seen. In the epithelium the lipoid is present practically throughout the cells. In the cytoplasm between the nucleus and the free border it occurs as small granules, and as the basement membrane is approached these granules seem to grow only in the deepest portions of the cells, where they form large, globular, fat-filled vacuoles.

It is intended that this paper be quite brief and mainly pictorial, for the illustrations are so decisive that that they speak for themselves.

Fig. 276 shows the general appearance of the interior of the gall-bladder, with extensive lipoid infiltration and several polyps.

Fig. 277 is a low-power section of one of the polyps, showing that it consists almost entirely of a tightly-packed collection of lipoid-containing cells.

Fig. 278 is a water-colour drawing of a very small area of the polyp and shows the very rich infiltration of stromal macrophages in addition to infiltration of the epithelial cells.

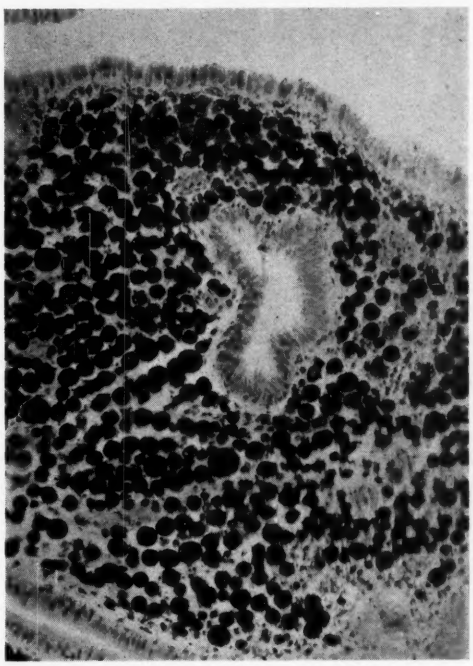

FIG. 280.—Cholesterosis of the gall-bladder. Section of polyp, stained hæmatoxylin-Scharlach R (high power). The section is of an area of gall-bladder wall where cholesterol deposit is exceedingly rich. It concerns principally the globular 'foam cells' of the mucosal connective tissue; but the epithelium, especially of the centrally situated glandular space, shows in addition some granular lipoid deposit.

Fig. 279, on the other hand, represents an area of non-polypose mucous membrane and here the epithelial infiltration is even more abundant. The exceedingly important observation to be made on *Figs.* 278 and 279 is that the epithelial lipoid occurs as rows of globules, graduated in size, the largest being nearest to the basement membrane of the cells, the finest near the free border, and that the free border itself is actually free of visible lipoid.

Figs. 280 and 281 are photomicrographs of a section of the polyp and confirm the features illustrated in these drawings, and *Fig.* 282 is a picture taken through crossed Nicol prisms showing the doubly-refracting crystalline lipoid in the stromal macrophages.

Fig. 283 is a higher-power view of a small area of mucosal epithelium, showing again the gradation of the lipoid globules, these becoming larger as the basement membrane is approached.

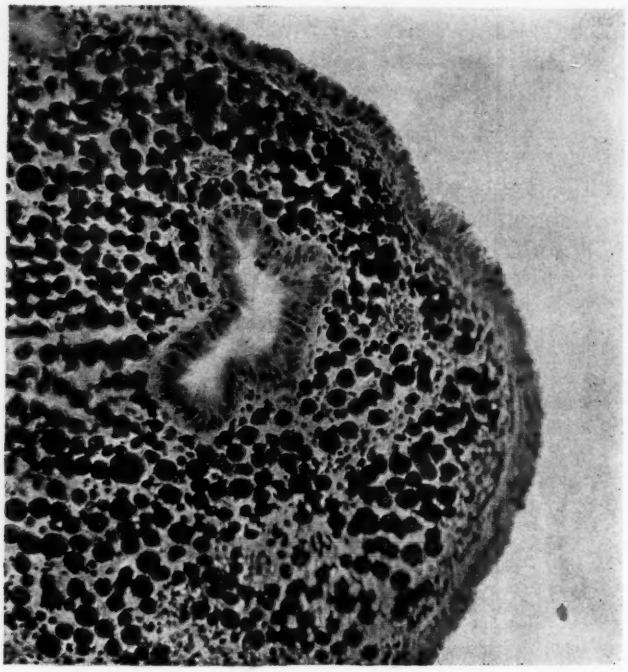

FIG. 281.—Cholesterosis of the gall-bladder. Dufay colour photomicrograph of section stained hæmatoxylin-Scharlach R (high power). This picture illustrates well the rich lipoid infiltration, both of the stromal macrophages and of the epithelium, especially of the centrally situated glandular pocket.

FIG. 282.—Cholesterosis of the gall-bladder. Section of polyp, stained hæmatoxylin-Scharlach R (high power). Doubly refracting lipoid. This area of gall-bladder wall (the same as that shown in *Fig.* 280), has been photographed through crossed Nicol prisms. It will be seen that a large amount (though not all) of the lipoid in the stromal macrophages is doubly refracting, and in addition to showing brilliant illumination it illustrates the 'fluid-crystalline' nature of this doubly refracting fat. There are no doubly refracting points in the epithelium, and this is a noteworthy feature of the specimen. Thorough widespread search failed to demonstrate any doubly refracting lipoid in the mucosal epithelium.

These histological observations support those made by Policard in 1914, and quoted in the earlier paper. The whole picture indicates that lipoid matter in solution is being resorbed from the bile, that it is gradually concentrated in globules, and that finally it is carried off by the lymphatics. The whole process is parallel with that carried out by the analogous intestinal epithelium, and with the active resorption of other substances known to be carried out normally by the gall-bladder lining. Under certain conditions, e.g., when the bile is unusually rich in fat, the

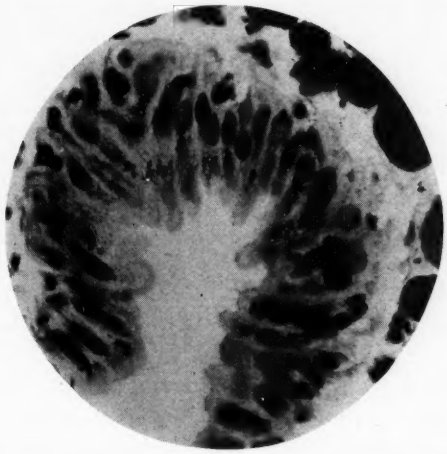

FIG. 283.—Photomicrograph (high power) of mucous membrane of gall-bladder, stained hæmatoxylin-Scharlach R. Lipoid (darkly stained) is seen both in the epithelial cells and in the connective tissue. In the epithelial cells it appears as tiny granules, of which the smallest are toward the free border. In the stroma the lipoid is distending the large globular 'foam cells', which stain intensely.

lipoid in transit through the gall-bladder wall becomes visible to the naked eye. Under others it may be stored for a time in stromal macrophages. It is reasonable to suppose that where polyps are present the lymphatics of the tenuous pedicle have difficulty in handling the lipoid absorbed by the great area of the mucosa of the polyp and that as a result excessive stromal deposit takes places.

Summary and Conclusions.—Histological study of a specimen of cholesterosis of the gall-bladder with cholesterol polyps confirms the view that cholesterosis is due to a process of resorption of lipoid from the bile in the lumen of the gall-bladder.

My thanks are due to Mr. Roy F. Young, Surgeon to the Western Infirmary, for permission to publish this case; to Dr. A. C. Lendrum and Dr. T. W. Govan, of the Pathological Institute, University of Glasgow, for their histological work; to Dr. J. S. Fulton for the cholecystograms; to Miss Cecily Brown Kelly for the water-colour drawings; and to Mr. John Kirkpatrick for the photomicrographs.

REFERENCE

MACKEY, W. A., "Cholesterosis of the Gall-bladder; A Review, Supplemented by Personal Observations on 87 Cases", *Brit. Jour. Surg.*, 1937, **24**, 570.

NUTRITIONAL ŒDEMA AS A COMPLICATION OF JEJUNOCOLIC FISTULA

By S. DE NAVASQUEZ

FROM THE DEPARTMENT OF PATHOLOGY, GUY'S HOSPITAL MEDICAL SCHOOL

THE role played by the plasma proteins, and particularly by the serum albumin, in maintaining the normal interchange of fluid in the body by virtue of their osmotic pressure, first demonstrated by Starling (1896), is now generally accepted. The first direct proof that œdema could be produced in otherwise normal animals by lowering the plasma-protein concentration was obtained by Leiter (1928) by means of plasmapharesis.* Œdema and ascites occurred regularly when the plasma proteins had been reduced to, and maintained at, about the critical level of 3 g. per cent. This experimental œdema, in the absence of cardiac or renal disease, strongly supported the view that the 'famine' œdema so prevalent in Central Europe during the Great War was due to the marked diminution in the plasma proteins resulting from the insufficiency of the protein in the food. Leiter's suggestions as to the pathogenesis of this variety of œdema received confirmation when Bruckman, D'Esopo, and Peters (1930) showed that in malnutrition in man œdema always developed when the serum albumin fell below 3 per cent. While the occurrence of nutritional œdema is well recognized in chronic disease in which starvation was produced naturally or intentionally, as was the case in a former treatment of diabetes, we have been unable to find any record in the literature of such a complication as a result of jejunocolic fistula. For this reason, and because of the peculiar changes in the gastro-intestinal tract which were responsible for the inanition, the following case appears to be worthy of being recorded.

CASE REPORT

Frederick B., aged 55, a warehouseman, was admitted on May 7, 1939, under Sir Arthur Hurst, for œdema of the lower extremities. His family history was not relevant.

After a normal school life, he joined the Royal Navy at the age of 14 and he remained in good health until 1921, when he developed a duodenal ulcer which was treated by gastro-jejunostomy, from which he made an uneventful recovery. He remained well until 1933, when he complained of a recurrence of his abdominal pain; he was admitted to hospital with a diagnosis of gastrojejunal ulcer, which was treated dietetically for sixteen weeks, after which he was discharged as fit. Since 1933 he had had intermittent attacks of abdominal pain which was relieved by alkalis. His consumption of alcohol and tobacco was 3 pints of beer daily and a pound of pipe tobacco monthly.

He denied any history of rheumatic fever or tropical or venereal disease.

He first noticed swelling of the ankles four weeks before admission; it was of sudden onset, but gradually spread upwards to involve the thighs, abdomen, and chest, and has persisted since.

ON EXAMINATION.—There was severe subcutaneous œdema which extended from the ankles to the clavicles and which involved the scrotum, penis, and lumbar region. There was marked wasting of the face and supraclavicular fossæ.

* Plasmapharesis: bleeding of experimental animals, removing the plasma proteins, and returning the washed red cells to the circulation.

Cardiovascular system: The pulse-rate was regular and 84 a minute; the blood-pressure was 122 mm. Hg systolic and 75 mm. diastolic; no abnormality was detected in the heart.

Respiratory system: The chest moved poorly and a few râles and rhonchi were heard at both bases.

Alimentary system: The abdomen was distended by ascites which gave a fluid thrill and shifting resonance; the abdominal viscera were not palpable or tender.

Central nervous system: The retinæ and all the reflexes were normal.

Genito-urinary system: The penis and scrotum were œdematous; the urine was of a specific gravity of 1032, acid, and devoid of any abnormal constituents.

Special Investigations.—Radiography: Of the chest revealed no abnormality; of stomach and duodenum, "the stomach is short and meal leaves rapidly through gastro-jejunostomy but can be expressed through pylorus into duodenum. Neither was tender." Test meal showed hyperchlorhydria and the stomach emptied in 45 minutes. No abnormal constituents found.

Repeated examination of many samples of fæces failed to reveal occult blood or other abnormality.

The lævulose and glucose tolerance tests were normal.

The urea-concentration test was normal and repeated examination of the urine showed a normal daily output of high specific gravity and devoid of abnormal constituents.

Blood examination: Hæmoglobin, 68 per cent; red blood-cells, 3,230,000 per c.mm.; colour index, 1. The leucocytes were 7500 per c.mm. and the differential count was: polymorph leucocytes, 42 per cent; lymphocytes, 46 per cent; eosinophils, 1 per cent; basophils, 2 per cent; monocytes, 9 per cent. No abnormal cells were seen. Plasma proteins: "Total protein, 4·18 per cent; albumin, 1·82 per cent, globulin, 2·36 per cent. There is marked diminution in the plasma albumin and a reversal of the albumin-globulin ratio."

The Wassermann and Kahn reactions were negative.

Three days after admission, 1½ litres of clear fluid were withdrawn from the abdomen and a similar quantity on the two following days. The œdema persisted without fluctuation for ten days, when salyrgan, 1 c.c., was injected on two occasions at 48 hours' interval. This caused a marked diuresis, the urinary output being doubled in the following ten days, accompanied by diminution and finally disappearance of the œdema. The patient, however, began to complain of increasing weakness and drowsiness, and though the œdema had disappeared and the urinary output had returned to normal, he sank into coma and died thirty-six days after admission. He had been on a farinaceous diet throughout.

At Autopsy (P.M. No. 186, 1939).—External appearance: A middle-aged male of slight build, with an old surgical paramedian abdominal scar, and showing extreme wasting and dehydration. There was no œdema. Height, 5 ft. 5 in.

Cardiovascular system: The heart weighed 200 g. and showed severe brown atrophy, the myocardium being uniformly reduced in thickness, brown, and firm; there were no endocardial or valvular abnormalities, and the aorta was of normal dimensions and elasticity and entirely devoid of atheroma; the coronary arteries were more tortuous than normal and free from atheroma.

Respiratory system: The larynx, trachea, and bronchi were normal; the pleuræ and lungs were abnormally dry, but otherwise normal.

Alimentary system: The mouth, tongue, tonsils, fauces, pharynx, and œsophagus were normal; the stomach was distended with gas, bile-stained fluid, and partially digested food. Apart from post-mortem autolysis around the cardiac orifice, the mucous membrane was normal throughout. A gastrojejunal stoma 6 cm. in circumference was present on the posterior wall, 3 cm. proximal to the pyloric ring, the latter being normal. The duodenum, 1 cm. below the pyloric ring, showed a flat, smooth, and rounded scar on the posterior wall, but was otherwise normal. The duodeno-jejunal flexure and the jejunum for the first 12 cm. were normal. At this point the jejunum became attached to the middle of the transverse colon by dense smooth fibrous tissue, which completely surrounded a fistulous communication between the two. The fistulous stoma measured 7 cm. in circumference and was situated below and directly opposite the gastrojejunal stoma. The mucous membrane on the jejunal side of the jejunocolonic fistula was normal, but that of the colon showed a

CHOLESTEROSIS OF THE GALL-BLADDER
A FURTHER CONTRIBUTION TO THE HISTOLOGY OF THIS CONDITION

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CHOLESTEROSIS of the gall-bladder, appositely termed 'strawberry gall-bladder' because of the yellow stippling of the gall-bladder lining, is a condition due to infiltration of the mucous membrane with lipoid which is in large measure doubly refracting. The infiltration affects both lining epithelium and subepithelial tissue in varying degree. In the past there has been acute difference of opinion upon the nature of the mechanism involved, whether the lipoid is in process of excretion into the lumen of the gall-bladder or has been taken up from the bile. The subject was reviewed by the writer recently (1937), and it was shown that the balance of the available evidence indicates that cholesterosis of the gall-bladder is probably simply a 'visualization' of a normal process of resorption of lipoid and fat from the bile. It is unnecessary to repeat the arguments stated then, and as there has been no important subsequent contribution, the present paper may be considered as a postscript to the earlier review.

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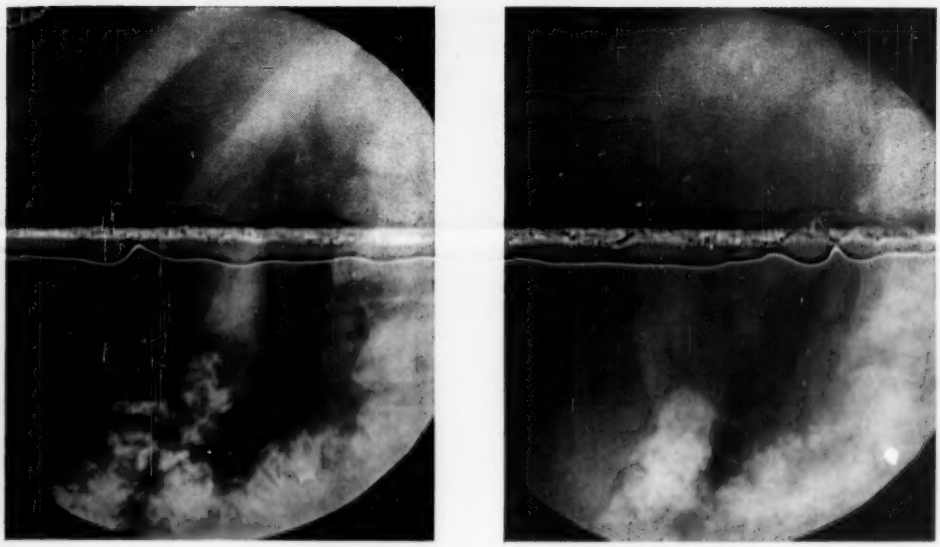

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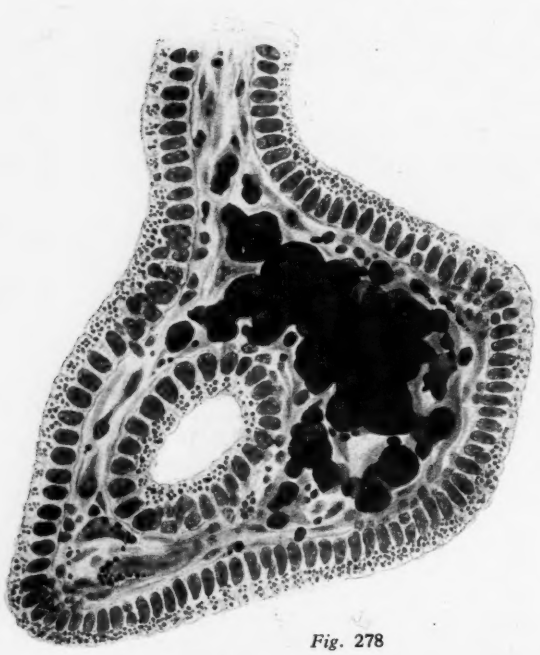

Fig. 278

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FIG. 278.—Water-colour drawing of portion of cholesterol poylp, stained hæmatoxylin-Scharlach R. There is a rich deposit of lipoid (staining brightly red) principally in the connective tissue, and to a lesser extent in the mucosal epithelium. In the connective tissue all stages of lipoid storage may be seen from the appearance of a few globules in macrophage cells, indistinguishable from ordinary connective-tissue cells, to fully formed 'foam cells' enormously blown out with finely emulsified fat. In the columnar epithelium the lipoid distribution is uniform and noteworthy. Lipoid occurs in the clear portion of the columnar cells distal to the nucleus as globules and granules of various size arranged in a fairly regular gradation, with the smallest near the free border of the cell.

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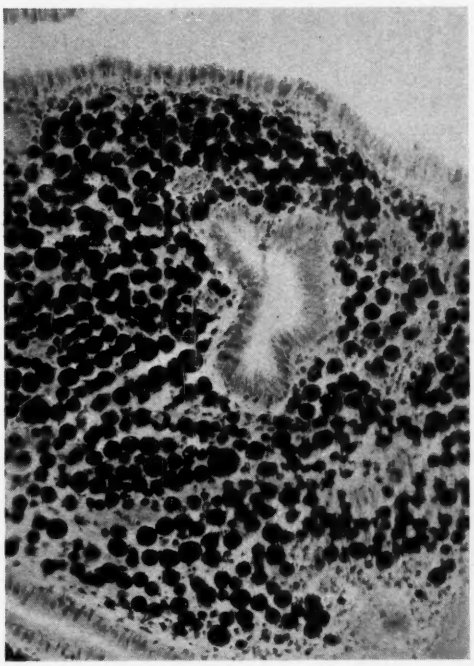

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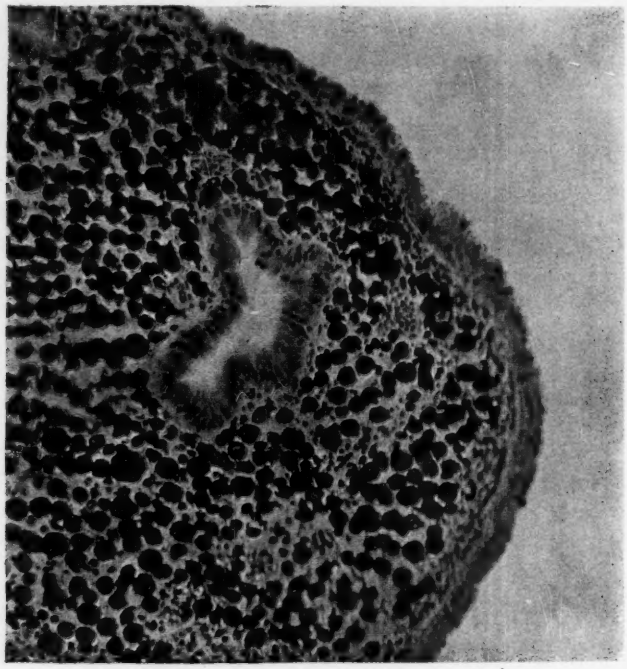

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FIG. 282.—Cholesterosis of the gall-bladder. Section of polyp, stained hæmatoxylin-Scharlach R (high power). Doubly refracting lipoid. This area of gall-bladder wall (the same as that shown in *Fig.* 280), has been photographed through crossed Nicol prisms. It will be seen that a large amount (though not all) of the lipoid in the stromal macrophages is doubly refracting, and in addition to showing brilliant illumination it illustrates the 'fluid-crystalline' nature of this doubly refracting fat. There are no doubly refracting points in the epithelium, and this is a noteworthy feature of the specimen. Thorough widespread search failed to demonstrate any doubly refracting lipoid in the mucosal epithelium.

These histological observations support those made by Policard in 1914, and quoted in the earlier paper. The whole picture indicates that lipoid matter in solution is being resorbed from the bile, that it is gradually concentrated in globules, and that finally it is carried off by the lymphatics. The whole process is parallel with that carried out by the analogous intestinal epithelium, and with the active resorption of other substances known to be carried out normally by the gall-bladder lining. Under certain conditions, e.g., when the bile is unusually rich in fat, the

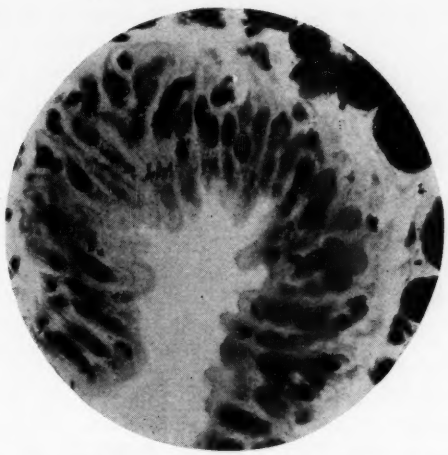

FIG. 283.—Photomicrograph (high power) of mucous membrane of gall-bladder, stained hæmatoxylin-Scharlach R. Lipoid (darkly stained) is seen both in the epithelial cells and in the connective tissue. In the epithelial cells it appears as tiny granules, of which the smallest are toward the free border. In the stroma the lipoid is distending the large globular ' foam cells ', which stain intensely.

lipoid in transit through the gall-bladder wall becomes visible to the naked eye. Under others it may be stored for a time in stromal macrophages. It is reasonable to suppose that where polyps are present the lymphatics of the tenuous pedicle have difficulty in handling the lipoid absorbed by the great area of the mucosa of the polyp and that as a result excessive stromal deposit takes places.

Summary and Conclusions.—Histological study of a specimen of cholesterosis of the gall-bladder with cholesterol polyps confirms the view that cholesterosis is due to a process of resorption of lipoid from the bile in the lumen of the gall-bladder.

My thanks are due to Mr. Roy F. Young, Surgeon to the Western Infirmary, for permission to publish this case; to Dr. A. C. Lendrum and Dr. T. W. Govan, of the Pathological Institute, University of Glasgow, for their histological work; to Dr. J. S. Fulton for the cholecystograms; to Miss Cecily Brown Kelly for the water-colour drawings; and to Mr. John Kirkpatrick for the photomicrographs.

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NUTRITIONAL ŒDEMA AS A COMPLICATION OF JEJUNOCOLIC FISTULA

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THE role played by the plasma proteins, and particularly by the serum albumin, in maintaining the normal interchange of fluid in the body by virtue of their osmotic pressure, first demonstrated by Starling (1896), is now generally accepted. The first direct proof that œdema could be produced in otherwise normal animals by lowering the plasma-protein concentration was obtained by Leiter (1928) by means of plasmapharesis.* Œdema and ascites occurred regularly when the plasma proteins had been reduced to, and maintained at, about the critical level of 3 g. per cent. This experimental œdema, in the absence of cardiac or renal disease, strongly supported the view that the 'famine' œdema so prevalent in Central Europe during the Great War was due to the marked diminution in the plasma proteins resulting from the insufficiency of the protein in the food. Leiter's suggestions as to the pathogenesis of this variety of œdema received confirmation when Bruckman, D'Esopo, and Peters (1930) showed that in malnutrition in man œdema always developed when the serum albumin fell below 3 per cent. While the occurrence of nutritional œdema is well recognized in chronic disease in which starvation was produced naturally or intentionally, as was the case in a former treatment of diabetes, we have been unable to find any record in the literature of such a complication as a result of jejunocolic fistula. For this reason, and because of the peculiar changes in the gastro-intestinal tract which were responsible for the inanition, the following case appears to be worthy of being recorded.

CASE REPORT

Frederick B., aged 55, a warehouseman, was admitted on May 7, 1939, under Sir Arthur Hurst, for œdema of the lower extremities. His family history was not relevant.

After a normal school life, he joined the Royal Navy at the age of 14 and he remained in good health until 1921, when he developed a duodenal ulcer which was treated by gastro-jejunostomy, from which he made an uneventful recovery. He remained well until 1933, when he complained of a recurrence of his abdominal pain; he was admitted to hospital with a diagnosis of gastrojejunal ulcer, which was treated dietetically for sixteen weeks, after which he was discharged as fit. Since 1933 he had had intermittent attacks of abdominal pain which was relieved by alkalis. His consumption of alcohol and tobacco was 3 pints of beer daily and a pound of pipe tobacco monthly.

He denied any history of rheumatic fever or tropical or venereal disease.

He first noticed swelling of the ankles four weeks before admission; it was of sudden onset, but gradually spread upwards to involve the thighs, abdomen, and chest, and has persisted since.

ON EXAMINATION.—There was severe subcutaneous œdema which extended from the ankles to the clavicles and which involved the scrotum, penis, and lumbar region. There was marked wasting of the face and supraclavicular fossæ.

* Plasmapharesis: bleeding of experimental animals, removing the plasma proteins, and returning the washed red cells to the circulation.

Cardiovascular system: The pulse-rate was regular and 84 a minute; the blood-pressure was 122 mm. Hg systolic and 75 mm. diastolic; no abnormality was detected in the heart.

Respiratory system: The chest moved poorly and a few râles and rhonchi were heard at both bases.

Alimentary system: The abdomen was distended by ascites which gave a fluid thrill and shifting resonance; the abdominal viscera were not palpable or tender.

Central nervous system: The retinæ and all the reflexes were normal.

Genito-urinary system: The penis and scrotum were œdematous; the urine was of a specific gravity of 1032, acid, and devoid of any abnormal constituents.

Special Investigations.—Radiography: Of the chest revealed no abnormality; of stomach and duodenum, "the stomach is short and meal leaves rapidly through gastro-jejunostomy but can be expressed through pylorus into duodenum. Neither was tender." Test meal showed hyperchlorhydria and the stomach emptied in 45 minutes. No abnormal constituents found.

Repeated examination of many samples of fæces failed to reveal occult blood or other abnormality.

The lævulose and glucose tolerance tests were normal.

The urea-concentration test was normal and repeated examination of the urine showed a normal daily output of high specific gravity and devoid of abnormal constituents.

Blood examination: Hæmoglobin, 68 per cent; red blood-cells, 3,230,000 per c.mm.; colour index, 1. The leucocytes were 7500 per c.mm. and the differential count was: polymorph leucocytes, 42 per cent; lymphocytes, 46 per cent; eosinophils, 1 per cent; basophils, 2 per cent; monocytes, 9 per cent. No abnormal cells were seen. Plasma proteins: "Total protein, 4·18 per cent; albumin, 1·82 per cent, globulin, 2·36 per cent. There is marked diminution in the plasma albumin and a reversal of the albumin-globulin ratio."

The Wassermann and Kahn reactions were negative.

Three days after admission, 1½ litres of clear fluid were withdrawn from the abdomen and a similar quantity on the two following days. The œdema persisted without fluctuation for ten days, when salyrgan, 1 c.c., was injected on two occasions at 48 hours' interval. This caused a marked diuresis, the urinary output being doubled in the following ten days, accompanied by diminution and finally disappearance of the œdema. The patient, however, began to complain of increasing weakness and drowsiness, and though the œdema had disappeared and the urinary output had returned to normal, he sank into coma and died thirty-six days after admission. He had been on a farinaceous diet throughout.

At Autopsy (P.M. No. 186, 1939).—External appearance: A middle-aged male of slight build, with an old surgical paramedian abdominal scar, and showing extreme wasting and dehydration. There was no œdema. Height, 5 ft. 5 in.

Cardiovascular system: The heart weighed 200 g. and showed severe brown atrophy, the myocardium being uniformly reduced in thickness, brown, and firm; there were no endocardial or valvular abnormalities, and the aorta was of normal dimensions and elasticity and entirely devoid of atheroma; the coronary arteries were more tortuous than normal and free from atheroma.

Respiratory system: The larynx, trachea, and bronchi were normal; the pleuræ and lungs were abnormally dry, but otherwise normal.

Alimentary system: The mouth, tongue, tonsils, fauces, pharynx, and œsophagus were normal; the stomach was distended with gas, bile-stained fluid, and partially digested food. Apart from post-mortem autolysis around the cardiac orifice, the mucous membrane was normal throughout. A gastrojejunal stoma 6 cm. in circumference was present on the posterior wall, 3 cm. proximal to the pyloric ring, the latter being normal. The duodenum, 1 cm. below the pyloric ring, showed a flat, smooth, and rounded scar on the posterior wall, but was otherwise normal. The duodeno-jejunal flexure and the jejunum for the first 12 cm. were normal. At this point the jejunum became attached to the middle of the transverse colon by dense smooth fibrous tissue, which completely surrounded a fistulous communication between the two. The fistulous stoma measured 7 cm. in circumference and was situated below and directly opposite the gastrojejunal stoma. The mucous membrane on the jejunal side of the jejunocolonic fistula was normal, but that of the colon showed a

localized area of acute inflammation but without a breach of surface. The cæcum and ascending and transverse colon as far as the fistula were greatly distended with gas, bile-stained fluid, and a little soft fæces, and though the wall was thinned by distension, the mucous membrane was normal. The transverse colon beyond the fistula, the descending, pelvic, and sigmoid colon, and the rectum were of normal dimensions and contained a little bile-stained fluid only. The appendix was normal. The small intestine beyond the jejunocolic fistula was contracted and empty and the mucous membrane was normal. The mesentery showed a few small calcified nodules in the ileocæcal angle. The peritoneal cavity was dry and the peritoneum normal throughout.

Hepatic system: The liver weighed 1450 g. and was normal in every respect; the gall-bladder, biliary passages, and pancreas were normal.

Lymphatic system: The spleen weighed 80 g. and was atrophied; the inguinal, pelvic, para-aortic, and mediastinal lymph-glands were normal.

Genito-urinary system: The kidneys each weighed 150 g. and were of normal size and shape; the parenchyma was of normal width, pattern, colour, and consistency. The ureters and bladder were normal. The prostate and testes were normal.

Endocrine system: The thyroid was normal; the adrenals were normal.

Histological examination: The liver showed fatty change only; the kidneys were normal.

Anatomical diagnosis: Inanition due to jejunocolic fistula.

DISCUSSION

The main interest of this case lies in the pathogenesis of the œdema, which was the salient clinical feature. It was of the kind usually termed 'nephrotic', in that it was severe and unrelated to mechanical factors such as posture or exercise, and when this type occurs in Bright's disease, it is associated with marked albuminuria and consequent reduction in the plasma proteins.

As far as is known, the plasma proteins play no part in nutrition, their only known function being the maintenance of osmotic pressure by reason of their colloid nature, thus controlling the exchange of fluid between the blood and tissues. In this respect, albumin is the most important of the protein fractions because of its greater osmolar activity and higher concentration (Govaerts, 1926). The level of the plasma proteins remains remarkably constant under normal conditions and is not influenced by short periods of fasting or heavy protein feeding. After depletion by experimental measures they are regenerated even in the absence of protein intake, though regeneration is more rapid and complete on a protein diet; furthermore, there is considerable evidence to show that the liver is responsible for both the maintenance and regeneration of the plasma proteins (Kerr, Hurwitz, and Whipple, 1918–9).

A reduction of plasma albumin may be due to: (1) Loss by excretion, as in the albuminuria of Bright's disease; (2) Insufficient intake, as in the cases of prolonged malnutrition reported by Bruckman and Peters (1930); (3) Deficient absorption in pathological conditions in the gastro-intestinal tract, as in a case reported by Landis and Leopold (1930); and (4) Inadequate regeneration of proteins in certain diseases of the liver.

In the present case, the œdema was the direct result of the diminished serum albumin, which was 1·82 g. per cent, well below the normal range of 3·4–4·9 g. (Peters and Van Slyke) and also below the critical level of 3 g. per cent, at which figure œdema begins to appear (Bruckman, D'Esopo, and Peters). As for the cause of the low serum albumin, renal disease is excluded by the absence of albuminuria at any time and the constantly high specific gravity of the urine, nor is there any evidence to show that the intake of protein was insufficient, since the

last time he had been on a presumably protein-deficient diet for a long period was six years before the onset of his œdema. During his stay in hospital he had been on a mainly farinaceous diet, which may have diminished the rate of regeneration of the plasma proteins but could not have initiated their fall. A reasonable explanation is to be found in the changes in the gastro-intestinal tract. As a result of the wide jejunocolic fistula situated immediately below the gastrojejunostomy, food would naturally pass more readily into the colon than into the distal jejunum. The full dilated cæcum and colon as far as the fistula and the empty jejunum and ileum found at autopsy strongly suggest that this was the case, and that the short circuit eliminated the opportunity for the absorption of proteins from the small intestine. The by-passing of the small intestine by the passage of food into the transverse colon and cæcum may also afford an explanation for the absence of diarrhœa, which is a common feature of gastrocolic fistula, in that the food remained in the cæcum and colon sufficiently long to allow the absorption of water and the formation of firm fæces. The only sign of irritation in the colonic mucous membrane was a small localized area of inflammation opposite the fistula, which may well have been due to trickling of gastric secretion through the gastrojejunal stoma directly into the colon.

The subsequent course of the œdema is of some interest. It completely disappeared in ten days following the injection of salyrgan, which produced a marked diuresis lasting throughout the period, but the patient developed increasing drowsiness and weakness and died in a state of severe dehydration and inanition.

SUMMARY

1. A case of nutritional œdema due to a jejunocolic fistula is described.

2. The pathogenesis of the œdema is discussed, and it is concluded that it was the result of depletion of the plasma proteins due to insufficient absorption in the small intestine.

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EXPERIMENTAL SURGERY

ANTISEPTICS IN BRAIN WOUNDS

AN EXPERIMENTAL STUDY OF THE HISTOLOGICAL REACTION OF CEREBRAL TISSUES TO VARIOUS ANTISEPTIC SOLUTIONS

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SYNOPSIS

Introduction
Survey of Surgical Antiseptics
Experimental Methods:
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- Pathological examination

Summary of Experiments:
- *A.* Control series
- *B.* Antiseptics:
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  2. Coal-tar derivatives
  3. Halogen compounds
  4. Organic mercurial compounds
  5. Hydrogen peroxide
  6. Soluseptasine

Discussion
Conclusions

INTRODUCTION

The frequency with which compound injuries of the head occurred in the war of 1914–18, and are now seen in civil life as a result of the increasing toll of road accidents, calls for special attention to the details of their treatment. The liability of the brain to become infected as a result of such injuries and the often fatal character of cerebral infections justify an inquiry into the possible benefits that may be gained by the treatment of head wounds with suitable antiseptics. One of the principal criticisms of the use of antiseptics in the treatment of wounds lies in the allegation that they are more harmful to the tissues than to the bacteria. This criticism has special force for cerebral surgery because of the highly delicate nature of brain tissue. In this paper we are concerned principally with the local effects upon the brain and meninges of such antiseptics as have gained support in the treatment of wounds in general. Our object is to ascertain which, if any, of the surgical antiseptics whose germicidal potency is widely accepted, can be applied safely to the brain.

* Working for the Medical Research Council.

In the last war clinical experiences with the use of antiseptics in the prevention of infection in wounds of various parts of the body were often disappointing, and most surgeons rightly came to rely more on the thorough mechanical cleansing of wounds and the careful excision of all potentially infected tissues. These measures, together with judicious drainage of wounds, were followed so frequently by successful healing that the further study of antiseptics was neglected. The experiences of general surgery were reflected in the methods that were evolved for the treatment of gunshot wounds of the brain. That no unanimity was reached by surgeons as to the place of antiseptics in cerebral surgery is shown by a study of the literature of the war period. No surgeon considered that, in comparison with other measures, antiseptics played more than a minor role in the prevention of infection. In treating gunshot wounds of the brain Sargent and Holmes (1915) used 2 per cent iodine in spirit and also 1–40 carbolic acid in 5 per cent saline; Joll (1915) used 1–4000 biniodide of mercury; Cushing (1918) used dichloramine-T in oil; Newton and Brown (1919) used B.I.P.P.; but most surgeons do not mention what antiseptic lotions they employed on the brain. This attitude is still maintained, and two recent accounts of the treatment of craniocerebral injuries by such recognized authorities as Donald Monro (1938) and Geoffrey Jefferson (1939) also do not mention the use of antiseptics.

That antiseptics are of definite value in the prevention of infection in wounds has been proved conclusively by animal experimentation. Both in this country and in Germany many investigators (Neufeld, 1922; Schiemann and Wreschner, 1922; Browning, 1934; and others) have shown in mice and other animals that the application of antiseptics, particularly of the flavine group, to experimental skin wounds which have been inoculated previously with cultures of virulent organisms, will ward off infection and prevent death from septicæmia. These crucial experiments are of immense significance in the prophylaxis of infection arising in wounds involving the brain. In cerebral injuries it is usually difficult and often technically impossible to perform as complete a débridement as is possible in wounds involving skin, fascia, and muscles alone. This means that potentially infected cerebral tissues have often to be left in situ. In such cases sterilization of the wound can be effected only by chemotherapeutic methods of wound disinfection. Cushing's observation in the last war (1918) that most of the deaths following gunshot wounds of the brain were due to infection stresses the importance of taking every measure to combat this complication.

At this point it is necessary to draw attention to differences in the action of antiseptics in the presence of recent or potential infection and of established infection. All authorities are agreed that it is impossible to sterilize an obviously infected wound by the surface application of surgical antiseptics. In established infection the bacteria are firmly entrenched in the surrounding tissues and cannot be reached by surface medicaments. The main use of antiseptics in such circumstances should be as irrigating lotions or chemical debriding agents, leaving the natural defences of the body to overcome the infection. In cases of recent or potential infection, however, the problem is a different one, because here, as the animal experiments mentioned in the preceding paragraph have proved, surgical antiseptics can be brought into contact with the bacteria and thus effect chemical sterilization of the wound.

The ideal antiseptic for such a purpose should possess three properties: first, it should be a potent bactericidal agent, *in vivo* as well as *in vitro*; secondly, it

should be innocuous to the tissues locally; and thirdly, it should be harmless to the animal as a whole after absorption. Some of the factors concerned in satisfying these criteria will be briefly considered.

In vitro tests of bactericidal potency are insufficient for determining the efficiency of antiseptics when applied to tissues, although frequently they are all that are reported. Difficulty is often encountered in interpreting the results of these tests and applying them to clinical practice. It is not sufficient to note that the antiseptic has bactericidal and bacteriostatic properties in high dilutions; it should also be stable, rapid in action, miscible with serum without suffering serious deterioration of efficiency, and potent within the normal range of *p*H of the tissues. Unfortunately crucial demonstrations of bactericidal efficiency *in vivo*, as shown by tests of the ability to sterilize recently infected wounds in animals, are seldom performed.

The effects of individual antiseptics upon the tissues have also been imperfectly studied. Empirical methods of investigation, including instillation of antiseptics into the conjunctival sac, local injection into muscle or the peritoneal cavity, and intravenous injection of varying doses, seem to be the most popular. Clinical observations on the healing of wounds under treatment with antiseptics are frequently recorded, but are seldom adequately controlled. On the other hand, detailed histological studies of the effects of antiseptics on tissues are seldom undertaken, and when made they are often incomplete. Methods of tissue study which have been employed are:—

1. Observations of the action of antiseptics upon the mobility of leucocytes (Bond, 1916; Browning and associates, 1917; Fleming, 1917; Albert and associates, 1938).

2. Observations on the effects of antiseptics upon tissue cultures (Lambert, 1916; Mueller, 1919; Lambert and Meyer, 1926; German, 1929; Buchsbaum and Bloom, 1931; Wolff and Julius, 1939).

3. Histological observations on wounds treated with antiseptics, principally by members of the flavine series (Drummond and McNee, 1917; Bashford and associates, 1917; Bennett and associates, 1922; Blacklock, 1929).

4. Histological observations on the spinal cord, brain, and meninges following the injection of antiseptics into the subarachnoid space (Wegeforth and Essick, 1919; Levinson and Perlstein, 1931; Hama, 1933).

As far as we are aware no one hitherto has studied histologically the effects produced by antiseptics when applied locally to the brain.

A SURVEY OF SURGICAL ANTISEPTICS

In investigating individual antiseptics for their local effects upon the brain and meninges, we chose those which are considered to exhibit potent germicidal properties when applied to wounds in general. Their selection entailed a survey of the realm of surgical antiseptics.

1. Acridine Compounds.—The principal members of this group are acriflavine, neutral acriflavine or euflavine, proflavine, and rivanol. The last-named is popular on the Continent, but does not seem to be as efficient as the other members of the group (Laquer and associates, 1924). The flavines are relatively slow in action, but their antiseptic properties are not impaired by the presence of

serum. They have long been held to be innocuous to the tissues (Browning and associates, 1917 and 1934; Bennett and associates, 1922; Garrod and Keynes, 1937), although this claim has been disputed repeatedly (Fleming, 1917 and 1938; Bashford and associates, 1917; Wegeforth and Essick, 1919; Eggerth, 1926; and others). However, their bactericidal efficiency *in vivo* has been conclusively demonstrated by crucial chemotherapeutic experiments in animals (Neufeld, 1922; Schiemann and Wreschner, 1922; Browning, 1934; and others). Recently Albert and his associates (1938) have shown that one other member of the acridine series, 2 : 7 diaminoacridine hydrochloride, has antiseptic properties equal if not superior to proflavine, and yet is even less toxic to leucocytes. This substance was therefore included in our investigations.

2. Coal-tar Derivatives.—As a group the phenols and cresols, in the concentrations in which they exhibit satisfactory germicidal activity, are too caustic for application to tissues (Garrod and Keynes, 1937). Recently emulsions of tar acids, which are more bactericidal and less caustic than the phenols and cresols, have received increasing attention. One of these, dettol, is a halogen derivative of xylenol dissolved in a mixture of aromatic essential oils. The oils are dissolved in a neutral solution of a suitable soap to render them miscible with water, thus forming a permanent emulsion when diluted with water or spirit. It has been shown to be a potent bactericidal and antiseptic agent on the unbroken skin, and will act in the presence of pus (Colebrook and Maxted, 1933). Through the courtesy of the manufacturers, Messrs. Reckitt & Colman, we were also able to test a 'modified' dettol which differs mainly in the quality of its soapy basis. It is less alkaline than ordinary dettol (*see* p. 486).

Supersan is a similar product prepared by Boots Pure Drug Co. Its active principles are, amongst other substances, chlor-meta-xylenol together with selected pine oils.

We tested these three emulsions in the strength recommended for application to wounds—5 per cent (Garrod and Keynes).

3. Halogen Compounds.—The great disadvantage of the halogen antiseptics is that, although they act rapidly *in vitro*, as a group (iodine and hypochlorites) they are inactivated by serum (Garrod and Keynes, 1937, and others). Dichloramine-T and iodoform are insoluble in water and therefore in serum. However, two water-soluble organic chlorine compounds, chloramine-T and azochloramid, are relatively stable in the presence of serum. *In vitro* tests have shown that in such circumstances azochloramid retains its antiseptic activity better than chloramine-T (Schmelkes and Horning, 1935; Winkler, 1938), and therefore azochloramid was selected for further study. Eusol was included, not because of its antiseptic powers, which are suppressed by serum, but because of the popularity of the hypochlorites as irrigating lotions and chemical debriding agents in established infections.

4. Salts and Compounds of Heavy Metals.—The principal germicidal agents in this group are compounds of silver and mercury. Their action is slow, and, in the concentrations ordinarily used, is impaired further by serum (Garrod and Keynes, 1937). Mercurochrome, formerly one of the most popular, has been shown to be one of the least efficient (von Oettingen and associates, 1932). Within recent years three organic mercurial compounds, metaphen—4-nitro-5-hydroxymercuri-ortho-cresol (Raiziss and associates, 1930; Birkhaug, 1930); merthiolate—

sodium-ethyl-mercuric thiosalicylate (Powell and Jamieson, 1931); and phenyl mercuric nitrate (Weed and Ecker, 1931; Birkhaug, 1933) have received prominence in the United States as efficient surgical antiseptics capable of acting in high dilutions, even in the presence of serum. We therefore selected these substances for further investigation.

5. Oxidizing Agents.—All these substances are inactivated rapidly by serum, and are, therefore, of little value as antiseptics. Hydrogen peroxide has, however, a marked popularity in neurosurgery as a hæmostatic and cleansing agent. For this reason it was included in our investigations.

6. Sulphonamide Compounds.—These substances differ from true antiseptics. As shown by many workers sulphonamide compounds act on the streptococcus *in vitro* when the organisms are relatively few, but have little effect when they are abundant. For this reason the local use of sulphonamide in the treatment of infected wounds has been discouraged. There is, however, no agreement as to the manner in which these compounds exert their action on bacteria. The theory that they are only effective after entry into the blood-stream is questionable, though they are undoubtedly active in the presence of blood. Jensen, Johnsrud, and Nelson (1939) described satisfactory results in the local treatment of potentially infected compound fractures with crystalline sulphanilamide. They were similarly able to protect guinea-pigs in which the ribs had been fractured and inoculated with cultures of *Staphylococcus aureus hæmolyticus*.

Soluseptasine (M & B 137) has been given intrathecally in the treatment of purulent leptomeningitis, but it cannot be claimed that cures have been achieved thereby, since it has also been given by other routes in these cases. It has been tested by us because it is one of the more soluble and more easily buffered members of this group.

EXPERIMENTAL METHODS

Operative Procedure.—Adult rabbits were used. The fur over the top of the head was removed by means of a depilatory paste. The skin was sterilized with corrosive sublimate solutions followed by alcohol. Anæsthesia was induced by the intravenous injection of a solution of nembutal supplemented when necessary by the inhalation of a few drops of ether. Under aseptic conditions a midline incision (usually from 4 to 5 cm. long) was made through the scalp. *On the left side* of the skull the pericranium was reflected medially as a triangular flap, and the bone trepanned with a drill and burr. Next the burr opening was enlarged by means of bone-nibbling forceps until a triangular decompression opening (averaging 2 cm. long by 1 cm. wide) had been made over the centre of the left cerebral hemisphere (*Fig.* 284). The underlying brain was then exposed by incising the dura in a stellate manner and reflecting the flaps. Accidental trauma to the surface of the brain was carefully avoided, the operative field being kept clean by irrigation with isotonic saline. After three or four minute scratches with the point of a needle had been made in the leptomeninges, neatly fitting pieces of lintine, soaked in the antiseptic solution which was being tested, were placed on the exposed surface

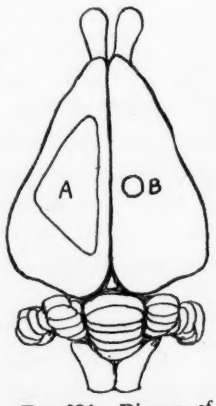

FIG. 284.—Diagram of rabbit's brain. A, Site of decompression; B, Site of burr hole.

of the brain for ten minutes. Usually these lintine soaks were changed once or twice during this period so as to ensure that an excess of antiseptic solution was maintained in contact with the brain. In a few experiments a linear incised wound (a few millimetres deep and up to 1 cm. long) was made in the exposed cortex with a scalpel, care being taken to avoid arterial arcades and not to enter the ventricle by too deep an incision. A thin wedge of lintine, soaked in antiseptic solution, was then placed between the lips of the incision before the surface lintine soaks were placed over the whole of the exposed cortex.

In all experiments, besides applying the antiseptic solutions to the surface of the brain we injected a small quantity of antiseptic solution into the cortex or white matter of the cerebral hemisphere. In our earlier experiments this was done by making a second burr hole through the centre of the parietal region *on the right side* of the skull. Then by means of a finely-graduated 'tuberculin' syringe and a No. 25 gauge needle, the point of which was directed laterally and slightly ventrally through the exposed dura, 0·2 c.c. of the antiseptic solution was injected into the brain. Usually some of the injected fluid leaked back to the surface along the needle track, either during the injection or after the needle had been withdrawn. This was interpreted as evidence that the injection had not penetrated into the ventricle, and autopsies subsequently disclosed that in the majority of experiments we had placed the injection in the white matter beneath the cortex and yet superficially to the ventricle. In some there was histological evidence that part of the fluid penetrated the leptomeningeal spaces towards the ventral and posterior surfaces of the right cerebrum. In a few animals these intracerebral injections produced such severe degrees of necrosis and hæmorrhage in the right hemisphere that the cranial contents were pushed over to the left side, and a large cerebral hernia was forced through the left-sided decompression opening. This led us to modify our technique, and in our later experiments we discarded the intracerebral injection into the right hemisphere, and instead we injected under direct vision 0·1 c.c. of the antiseptic solution into the cortex at the anterior angle of the decompression on the left side. We found that, if the injection were correctly placed, some of the antiseptic solution would leak back to the surface alongside the needle.

In all our operations satisfactory hæmostasis was secured by simple surgical measures and without the use of diathermy current, which might have produced heat-coagulative effects in the tissues. In all cases the excess of antiseptic solution remaining on the surface of the brain was removed by absorption with cotton-wool pledgets. Next the dural and pericranial flaps were rolled back over the surface of the brain in order to afford some protection, but because of retraction they never covered it completely. Then the scalp incision was closed with interrupted sutures of fine silk, two layers of sutures being employed in the posterior part of the incision where the deeper layer approximated the cut edges of the divided occipital muscles. The majority of animals made speedy recoveries. All the scalp wounds healed rapidly without inflammation or sepsis. The animals were left for periods of one, two, four, or eight days before being killed.

Pathological Examination.—All the animals, except three that were found dead, were killed by inhalation of ether or chloroform. The tissues were at once perfused, through a cannula inserted into the aorta, with warm isotonic saline followed by 10 per cent formaldehyde, using as gentle a pressure as possible. The brain was then removed and, after being

hardened in formaldehyde, was divided into coronal slices about 2 mm. thick. Selected slices were embedded in paraffin and sections were stained with Ehrlich's hæmatoxylin and eosin, Weigert's iron hæmatoxylin and van Gieson's mixture, Weigert's fuchselin and neutral red, phosphotungstic acid hæmatoxylin, toluidin blue for Nissl's bodies, and by Loyez's method for myelin. In selected examples blocks were also cut on the freezing microtome and the sections were stained by Rio-Hortega's silver carbonate methods for microglia and neurofibrils.

The numbers allotted to the animals in the sections that follow have been rearranged for the sake of continuity; they do not represent the order in which the operations were performed.

SUMMARY OF EXPERIMENTS

Table I.—CONTROLS

SOLUTION	*p*H	NO. OF EXPERIMENTS	DEGREE OF REACTION IN BRAIN
Isotonic buffered saline	7·4	5	Very slight
Isotonic saline	7·0	4	Very slight
Isotonic saline	2·2	2	Slight
Isotonic saline	10·0	3	Slight
Distilled water	7·0	7	Considerable

Table II.—ANTISEPTICS TESTED

ANTISEPTIC	SOLUTION	*p*H	NO. OF EXPERIMENTS	DEGREE OF REACTION IN BRAIN
1. Acridine Compounds :				
Acriflavine	0·1% in distilled water	2·0	9	Severe
	0·1% „ isotonic saline	2·0	2	Severe
	0·1% „ buffered isotonic saline	7·2	2	Severe
Euflavine	0·1% „ „ „ „	7·2	3	Severe
	0·05% „ „ „ „	7·4	2	Severe
Proflavine	0·1% „ „ „ „	6·2	8	Very slight
2 : 7 diamino-acridine	0·1% „ „ „ „	6·2	2	Slight
2 Coal-tar Derivatives :				
Dettol	5·0% in distilled water	12·0	5	Severe
	5·0% „ buffered isotonic saline	7·4	3	Moderate
'Modified' dettol	5·0% „ isotonic saline	8·4	2	Moderate
	5·0% „ buffered isotonic saline	8·1	2	Moderate
Supersan	5·0% „ „ „ „	8·2	2	Moderate
3. Halogen Compounds :				
Azochloramid	0·03% in buffered isotonic saline	7·4	15	Variable
	0·2% „ triacetin	4·0	3	Severe
Eusol		9·0	4	Severe
4. Organic Mercurial Compounds :				
Metaphen	0·1% in buffered isotonic saline	10·0	2	Considerable
	0·04% „ „ „ „	10·0	2	Considerable
Merthiolate	0·1% „ „ „ „	10·0	2	Considerable
	0·04% „ „ „ „	10·0	2	Moderate
Phenyl mercury nitrate	0·08% „ isotonic saline	10·0	2	Considerable
	0·04% „ „ „	10·0	2	Moderate
5. Hydrogen Peroxide	3·0% in distilled water	4·0	2	Moderate
	3·0% „ buffered isotonic saline	7·4	3	Moderate
6. Soluseptasine	3·3% in isotonic saline	10·0	2	Slight
	3·3% „ buffered isotonic saline	7·4	2	Slight

Tables I and *II* summarize the experiments conducted in respect of the different antiseptics tested and the controls necessary for their interpretation. Except where it is otherwise specified later in the text, standard phosphate buffers were used in the preparation of the solutions.

A. CONTROL SERIES

Before we could assess the effects of the various antiseptics upon the brain it was necessary to perform control experiments to ascertain what effects were produced by our operative procedures, and by the solvents used in the preparation of the antiseptics. Certain incidental histopathological conditions were encountered and an appreciation of these also is necessary for the interpretation of our results.

Incidental Histopathological Conditions of the Brain in the Rabbit.—The incidental conditions encountered were of two types :—

1. *Meningo-encephalitis due to the Encephalitozoon cuniculi.*—This disease was found microscopically in 5 out of 98 rabbits. Fortunately its focal character and histological appearances are characteristic and are easily distinguishable from those to be discussed. There was no evidence that the reaction of the brain towards the antiseptic was modified by the presence of the disease.

2. *Focal Degenerative Changes in the Cortical Neurones.*—In the cerebral cortex of the rabbit the pyramidal cells frequently appear distorted and atrophied, such cells occurring singly or in groups. The cytoplasm and nuclei are deeply hæmatoxyphil and neither Nissl substance nor neurofibrils are clearly demonstrable. The cause of this alteration is unknown. It is so common as to be virtually constant in one part or another of the cerebrum and is not associated with any other histological abnormality. It appears to be quite independent of such factors as rapidity of fixation after death, type of fixative used, or subsequent treatment of the tissue. This patchy change in the cortical neurones offered great difficulties when analysing the lesser degrees of damage sustained by the neurones in our experiments. Little significance was attached therefore to changes of this type, and our comparisons of the antiseptics have been based upon the grosser effects shown by the neurones, such as severe or widespread degeneration and necrosis.

Observations on the Effects of the Operative Procedures.—At operation we always made a few minute scratches in the leptomeninges to allow the antiseptic to enter the subarachnoid space. In addition we injected a little of the antiseptic into the cortex, and in a few instances made a small incision into the cerebrum. In order to estimate the degree of trauma inflicted by these measures we substituted isotonic saline buffered to *p*H 7·4 for the antiseptic in 5 rabbits. In 2 of these an incision was made in the cortex. We also injected ordinary isotonic saline (*p*H 7) into the cortex in 4 rabbits. All remained well after the operation.

Results: The leptomeninges at the site of operation showed slight focal hæmorrhage (*Fig.* 285) and reactive inflammation in the early stages. Later on fibroblastic proliferation was observed. The cortex was unaffected except for shrinkage, hyperchromatosis, and distortion of a moderate number of superficial neurones. Necrosis of neurones was rare. Considerable hæmorrhage, fragmentation, and necrosis of tissue accompanied the incised wounds. The puncture wound was recognized as a linear hæmorrhagic streak (*Fig.* 286) which, microscopically, was surrounded by a narrow zone of œdematous tissue containing reacting microglial cells. In one instance a superficial wedge of hæmorrhagic softening was found at the site of puncture, apparently the result of damage to a perforating vessel.

Herniation.—Removal of a portion of the skull was usually followed by a variable degree of protrusion of the brain. In most instances this developed later into a hernia, which sometimes reached the height of 0·6 cm. As a result, certain

FIG. 285.—Dorsal view showing moderate herniation and a few hæmorrhages on left side two days after application and injection of buffered isotonic saline (*p*H 7·4).

FIG. 286.—Effect of injection of buffered isotonic saline (*p*H 7·4) after two days. (H. & E.) (× 19.)

histological changes, usually slight, are produced in the cortex and white matter. To illustrate these we produced a hernia by decompressing the left cerebrum and injecting 0·2 c.c. of eusol into the right cerebrum.

Results: The hernia, four days later, was 0·4 cm. high (*Fig.* 287). The leptomeninges over it contained areas of hæmorrhage and moderate leucocytic

FIG. 287.—Hæmorrhage in meninges over hernia and changes in subjacent white matter. (H. & E.) (× 7.)

infiltration. There were a few small hæmorrhages in the marginal glia, accompanied by an increase in number and activity of microglial cells. The cortex was œdematous, and most of the superficial neurones were shrunken, hyperchromatic,

and distorted. At the anteromedial border of the hernia was a narrow wedge of hæmorrhagic necrosis which extended deeply into the cortex. This appeared to be due to pressure from the adjacent bony margin of the decompression. Areas of hæmorrhage and early cavitation were also present in the white matter at the base of the hernia.

These experiments show collectively that the effects of trauma inflicted by our operative procedures are relatively slight. In the leptomeninges there are focal hæmorrhages with proportionate inflammatory reaction. In the cortex œdema and diffuse microglial activity are present throughout the exposed area, while degeneration is confined to the superficial neurones. When herniation is present focal changes of a more severe character may arise through compression of the cortex against the bony margin of the decompression. The changes in the white matter at the base of the hernia were seen in all the moderate and severe hernias examined, but, as these changes are referable to the mechanical effects of hernia formation and not to the action of antiseptics, we shall not allude to them again in this paper.

Focal changes invariably accompany puncture wounds and are usually limited to a narrow zone about the needle track. The injection of approximately neutral isotonic saline is not demonstrably more destructive than puncture alone, the effects of which are already well known (Rio-Hortega and Penfield, 1927). Occasionally the injection may cause serious hæmorrhage and necrosis either by injury to one of the perforating vessels of the cortex or through forcing fluid into the tissues; this was seen in one of this group.

Observations on the Effects of the Solvents.—With few exceptions we are not aware of any attempt on the part of manufacturers to provide antiseptic solutions which are both isotonic and neutral. In some instances claims to neutrality do not pass muster when the hydrogen-ion concentration is estimated. In respect of tonicity many antiseptics in clinical use resemble distilled water; this is not surprising since water rather than saline is often used in hospitals and clinics for preparing and diluting antiseptics. We therefore made a series of experiments to demonstrate the effects of variations in hydrogen-ion concentration and tonicity in the solvents.

1. *Variations in Hydrogen-ion Concentration.*—Apart from azochloramid the antiseptics tested in this investigation have been either strongly alkaline (coal-tar series and the organic mercurial compounds) or acid (acridine compounds), the range of *p*H varying from 2 to 12. We therefore investigated the effects produced by these extremes.

Buffered isotonic saline at *p*H 2·2 was applied to the surface and injected into the cerebrum in 2 rabbits. Similarly saline at *p*H 10 was used in 3 rabbits.

Results: In both groups the degeneration of the superficial neurones of the exposed cortex was greater than that found after using neutral saline; in many foci the neurones were necrotic. Occasionally small hæmorrhages were also present. The puncture wounds were not identified in two instances; in the others the histological effects were similar to those resulting from the injection of neutral saline. The damage was possibly greater at *p*H 2·2 than at *p*H 10, but the number of experiments was too small to form a definite conclusion.

2. *Variations in Tonicity.*—Although it might be concluded in advance that distilled water would prove highly damaging to the brain, we tested its effects in 7 animals to complete our controls.

Results: The surface of the exposed brain was flecked or suffused with blood; in one it was raw through the shedding of fragments of cortex into the wound. Microscopically there was fibrinoid necrosis with variable, sometimes intense, leucocytic infiltration of the leptomeninges. There was a variable amount of necrosis in the adjacent brain extending, in one example, to the wall of the lateral ventricle and associated with intense leucocytic infiltration. Sections stained by the Weigert-Gram method showed that this infiltration was not due to bacterial contamination. Injection of distilled water into the cerebrum caused a large circumscribed area of necrosis fringed with hæmorrhages and leucocytic infiltration. The adjacent tissues were œdematous, but the neurones beyond the borders of the necrosis were intact.

From these experiments it is clear that the application or injection of distilled water causes a variable amount of necrosis in the brain and is apt to excite a pronounced infiltration with leucocytes. The reactions are more severe than those seen with isotonic saline buffered to *p*H 2·2 or 10. The necroses are circumscribed and the structures outside their boundaries show little damage. The histological appearances suggest that the penetrating power of distilled water is slight. Probably the diluting effects of cerebrospinal fluid, blood, and tissue fluids lead to a rapid restoration of electrolytic equilibrium, thereby limiting the effects of the distilled water.

B. ANTISEPTICS

Our control experiments have indicated the desirability of achieving neutrality and isotonicity in any solution that is to be applied to the brain. In the following experiments we have in each group made our solutions isotonic and have attempted to bring them to a point as near neutral as possible. In a few groups we have also tested solutions in distilled water for purposes of comparison.

1. ACRIDINE COMPOUNDS

a. **Acriflavine.**—The sample used was obtained from Boots Pure Drug Co. We tested it as follows: 0·1 per cent in distilled water (*p*H 2), 9 animals; 0·1 per cent in isotonic saline (*p*H 2), 2 animals; 0·1 per cent in buffered isotonic saline (*p*H 7·2), 2 animals. The *p*H of the unbuffered solutions was found to be 2; the acriflavine tended to be precipitated when the *p*H was raised above 7·2.

Results: All three solutions caused severe hæmorrhagic necrosis wherever they came into contact with the brain or leptomeninges (*Fig.* 288). In two animals the damage was limited to the surface of the brain, possibly from defective penetration of the acriflavine beneath the arachnoid membrane. In the rest the necrosis was more extensive and often reached the wall of the lateral ventricle (*Fig.* 289). Fibrinoid necrosis of the blood-vessels and extravascular collections of fibrin filaments were present in the more severely affected areas. The cellular inflammatory reaction was slight in proportion to the destruction of tissue; in particular the emigration of leucocytes at all stages was scanty. The tendency of acriflavine to cause hæmorrhagic necrosis of the brain in the absence of direct trauma was shown by the effects produced in the ventrolateral aspect of the right cerebrum in two animals in which an injection had been made on this side. The dye had seeped through the leptomeninges to reach the ventral surface (*Fig.* 290). In two

other animals the injection reached the lateral ventricle, causing widespread degeneration and necrosis of the ependyma and choroid plexus. In one of these animals, moreover, the dye escaping from the fourth ventricle caused hæmorrhagic necrosis of the dorsolateral borders of the medulla oblongata. Evidence of the

FIG. 288.—Showing extensive hæmorrhage in both hemispheres four days after application and injection of 0·1 per cent acriflavine in buffered isotonic saline (*p*H 7·2).

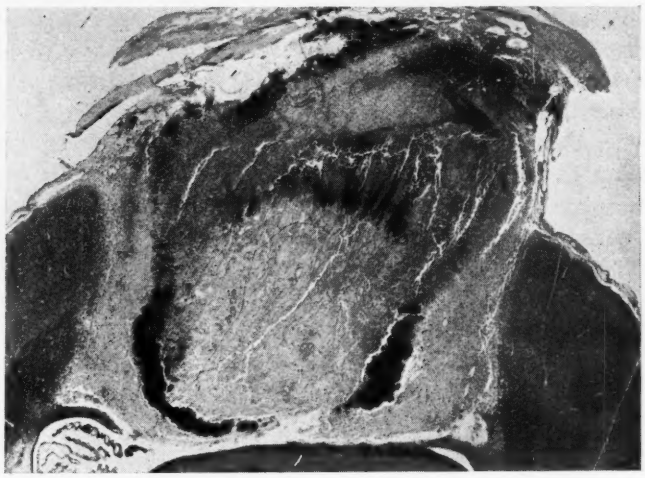

FIG. 289.—Severe necrosis of left cerebrum eight days after application of 0·1 per cent acriflavine in isotonic saline (*p*H 2). (H. & E.) (× 9.)

immediate destructive effect of acriflavine upon the ependyma was clearly shown by an additional experiment in which the animal died during the operation, apparently from an overdose of nembutal. Diffuse yellow staining of the ependyma

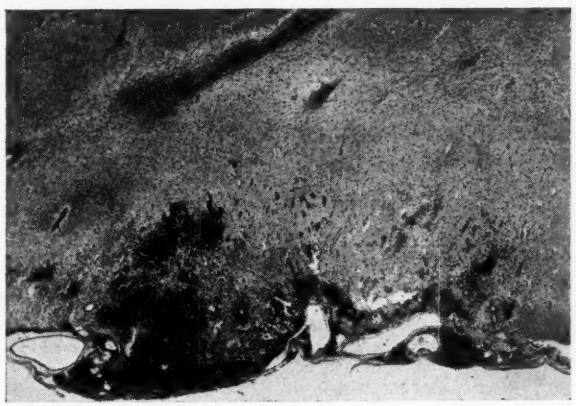

FIG. 290.—Ventrolateral border of right cerebrum, remote from site of injection of 0·1 per cent acriflavine in buffered isotonic saline (*p*H 7·2), showing extensive hæmorrhage. (H. & E.) (× 14.)

showed that the solution had been injected into the right ventricle. Microscopically the ependymal cells in many places had undergone dropsical swelling with loss of definition of their outlines and alterations in their cilia leading to fragmentation.

b. **Euflavine, or Neutral Acriflavine.**—The sample used was obtained from Boots Pure Drug Co. When dissolved it had a *p*H of 4 to 5. We tested it on 5 animals in 0·1 and 0·05 per cent solutions in isotonic saline buffered to *p*H 7·2 and 7·4 respectively.

Results: The reactions of the brain and leptomeninges to euflavine were similar to those observed with acriflavine. The effects were not conspicuously diminished by reducing the concentration to half strength. When introduced into the ventricles it caused degeneration of the ependyma and choroid plexus, but not in such severe degrees as with acriflavine.

c. **Proflavine Sulphate.**—We used this substance in a 0·1 per cent concentration in isotonic saline buffered to *p*H 6·2. The solutions were prepared from two separate stocks: (i) A 0·4 per cent dilution buffered to *p*H 6·2 and specially prepared for us by Boots Pure Drug Co.; (ii) A dry sample of commercial proflavine sulphate also obtained from Messrs. Boots. We found that the *p*H of an

FIG. 291.—Showing a few hæmorrhages in left cerebrum following application and injection of 0·1 per cent proflavine in buffered isotonic saline (*p*H 6·2).

FIG. 292.—Site of puncture two days after injection of 0·1 per cent proflavine in buffered isotonic saline (*p*H 6·2). (H. & E.) (× 19.)

unbuffered 0·1 per cent solution was less than 2, and that on neutralization the proflavine tended to be precipitated when the *p*H was raised to 6·5. Solution (i) was tested on 6 rabbits and solution (ii) on 2.

Results: The histological effects were remarkably slight. Macroscopically the exposed surface appeared normal or presented a few petechial hæmorrhages corresponding to points of scarification (*Fig.* 291). The puncture wound was usually represented by a streak of red corpuscles surrounded by a narrow zone of œdematous tissue, sparsely infiltrated in the earlier stages with leucocytes and later with increasing numbers of microglial cells (*Fig.* 292). In this zone a few neurones had undergone necrosis; neurones at its periphery showed chromatolysis, shrinkage, distortion, and occasionally pyknosis. After eight days advanced healing was in progress: the core of the track was occupied by spindle fibroblasts, microglial cells, and a few capillaries, while about it was a zone containing densely packed microglial cells, an excess of astrocytes, and well-preserved neurones (*Fig.* 293). In one example only, a wedge of necrosis extended through the cortex at the site of puncture. A similar instance occurred in our control series with normal saline (*see* p. 479),

and was probably due to trauma. There was little alteration of the cortex throughout the remainder of the operation area in all examples (*Figs.* 294, 295). A few of the superficial neurones were hyperchromatic, distorted, and shrunken, but necrosis

FIG. 293.—Showing healing of puncture wound eight days after injection of 0·1 per cent proflavine in buffered isotonic saline (*p*H 6·2). Compare with *Fig.* 289. (H. & E.) (× 14.)

FIG. 294.—Surface of cerebrum four days after application of 0·1 per cent proflavine sulphate in buffered isotonic saline (*p*H 6·2). Note adherent pericranium and narrow tongue of necrosis along perforating vessel (arrow). (H. & E.) (× 19.)

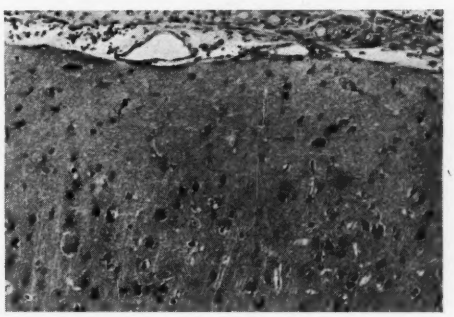

FIG. 295.—Central area from *Fig.* 294 showing slight degeneration of superficial neurones and excess of microglial nuclei beneath pia. (H. & E.) (× 80.)

was rare. The results thus closely resembled those obtained with neutral normal saline.

d. **2 : 7-Diaminoacridine Hydrochloride.**—This compound is one of the more recently synthetized members of the acridine series which were reported upon by Albert, Francis, Garrod, and Linnell (1938). They recommended it for clinical trial on account of its combination of high germicidal powers and relatively low toxicity. A sample of the dry solid was received from Glaxo Laboratories Ltd. Its *p*H when dissolved was 5. This, however, could be raised to 6·2 without precipitation, and we therefore used a 0·1 per cent solution in isotonic saline buffered to that point in experiments upon 2 animals.

Results: The effects were similar to those obtained with proflavine sulphate. There was, however, slightly more hæmorrhage both in the leptomeninges and in the subjacent cortex. Trial on a larger number of animals would be needed to maintain this distinction.

Summary.—Acriflavine, euflavine, proflavine sulphate, and 2 : 7-diaminoacridine have been tested. Of these the first two inflicted uniformly disastrous effects upon the brain: hæmorrhage and necrosis were conspicuous features. Adjustment of the tonicity and *p*H of the solutions did not bring about any appreciable improvement in the result. Likewise reducing the strength of the euflavine from 0·1 to 0·05 per cent had little effect. Proflavine sulphate and 2 : 7-diaminoacridine stand out in marked contrast to the first two compounds. The histological effects of proflavine, using a 0·1 per cent solution in isotonic saline buffered to a *p*H of 6·2, closely resembled those obtained with normal isotonic saline. We feel that 2 : 7-diaminoacridine deserves a more searching test than we were able to apply.

2. COAL-TAR DERIVATIVES

The solutions used were 5 per cent dilutions of (1) dettol and (2) 'modified' dettol (*see* p. 475), both supplied by Messrs. Reckitt & Colman; and (3) supersan (Boots Pure Drug Co.).

a. **Dettol.**—When diluted with distilled water dettol forms a milky emulsion the *p*H of which is 12. A 5 per cent solution in distilled water was applied to the surface of the cerebrum and injected into the cortex in 4 animals. Reduction of the *p*H to neutral point tends to disturb the emulsion, with the separation of oily droplets. A 5 per cent solution in isotonic saline was buffered to *p*H 7·4 and was well shaken before experimental application in 3 rabbits.

Results:

i. 5 *per cent in distilled water*: Severe fibrino-hæmorrhagic necrosis involved the leptomeninges at the site of exposure and extended into the subjacent cortex, reaching the wall of the lateral ventricle in all but one animal. The injection into the right cerebrum caused similar hæmorrhage and necrosis accompanied by great œdema of the surrounding tissues. In one animal the solution had penetrated to the posterior border of the hemisphere, causing hæmorrhagic necrosis of the leptomeninges and the adjacent cortex. In another animal, in which the injection had reached the lateral ventricle, both lateral ventricles were filled with blood. The ependyma, however, was intact except where it bordered the puncture wound.

ii. 5 *per cent in buffered isotonic saline*: There was fibrinoid necrosis of the greater part of the leptomeninges in the exposed areas. Meningeal hæmorrhage was focal and less severe than in (i). The subjacent cortex was infiltrated in early stages with leucocytes and later with microglial cells. Superficial neurones showed much distortion, shrinkage, and pyknosis, but necrosis was limited to a few foci. Considerable necrosis and hæmorrhage were found at the site of puncture in the right cerebrum. In one animal meningeal hæmorrhage and superficial necrosis of the cortex extended to the ventrolateral aspect of the right cerebrum.

b. **'Modified' Dettol.**—This differs from dettol in having a *p*H of 8·4 in unbuffered solutions. A 5 per cent solution in isotonic saline was injected into and applied to the surface of the cerebrum in 2 rabbits. On reduction of the *p*H there is a tendency, as with ordinary dettol, for oily droplets to separate. At *p*H 8·1 the emulsion appeared stable and no droplets were seen. A 5 per cent solution in isotonic saline buffered to this point was therefore used as before in 2 rabbits.

Results:

i. 5 *per cent in isotonic saline*: The exposed surface was injected and contained a few focal hæmorrhages. Fibrino-hæmorrhagic necrosis of the leptomeninges was

present at the site of puncture. Beneath this the cortex was occupied by a small wedge of hæmorrhagic necrosis surrounded by a zone of œdematous tissue containing a few perivascular hæmorrhages and leucocytes and in which the neurones showed stages of necrosis (*Fig.* 296). The remainder of the exposed cortex was normal apart from focal degeneration and necrosis of superficial neurones. A little subpial hæmorrhage was present in one animal.

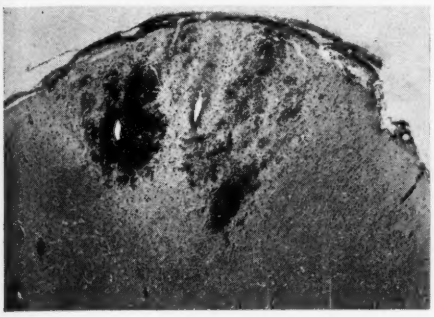

FIG. 296.—Showing wedge of necrosis and hæmorrhage two days after injection of 5 per cent 'modified' dettol in isotonic saline (*p*H 8·4). (H. & E.) (× 19.)

ii. 5 *per cent in buffered isotonic saline*: The results were similar to those in (i), but decidedly milder. The puncture wound was not identified in either animal, but its site was occupied by a few perivascular hæmorrhages about which the neurones showed stages of degeneration and necrosis. In the remainder of the exposed area the superficial neurones showed stages of degeneration but no necrosis.

COMMENT.—Dettol, in 5 per cent aqueous solution (*p*H 12), has a highly destructive effect upon the brain. Hæmorrhage and necrosis are both severe and lead to a marked swelling of the adjacent tissues. When rendered isotonic and buffered to *p*H 7·4 the amount of destruction is not excessive. The results obtained with 'modified' dettol are appreciably better. Thus the effects of an unbuffered solution in isotonic saline were not noticeably different from those obtained with the buffered solution of ordinary dettol. The isotonic buffered solution of 'modified' dettol was the least damaging of all: the results of injection were so slight that the wound evaded detection and the surface effects upon the brain were relatively trivial.

c. **Supersan.**—This preparation closely resembles 'modified' dettol in its physical properties, the *p*H of a 5 per cent solution being 9. An isotonic solution buffered to *p*H 8·2 appeared fairly stable. There was, however, a tendency for oily droplets to separate on standing; the solution was therefore well shaken before injection into and application to the surface of the cerebrum in 2 rabbits.

Results: The histological appearances were similar to those obtained with a buffered isotonic solution of 'modified' dettol. The site of puncture was represented in both animals by a linear hæmorrhage surrounded by a narrow zone in which the tissue was œdematous and infiltrated with a few leucocytes and microglial cells. Degeneration and necrosis of neurones was confined to this zone. In the remainder of the exposed cortex the superficial neurones showed stages of degeneration but no necrosis.

Summary.—Dettol, 'modified' dettol, and supersan have been tested. Dettol when diluted with distilled water causes extensive hæmorrhage, necrosis, and swelling of the brain. The effects are strikingly reduced by substituting isotonic saline for distilled water and buffering the solution to neutral point. 'Modified' dettol when similarly tested is superior to ordinary dettol. The effects of supersan are similar to those of 'modified' dettol and are little more severe than controls in which normal neutral saline is used.

3. HALOGEN COMPOUNDS

a. **Azochloramid (N-N-dichlorazodicarbonamide).**—Two samples were supplied by Messrs. Wallace & Tierman: (1) Tablets combining the compound with buffering salts, yielding a 0·03 per cent isotonic solution at *p*H 7·4 when dissolved in distilled water; and (ii) A 0·2 per cent solution in triacetin (*p*H 4). Tests were made with both, solution (i) being used in 15 animals and solution (ii) in 3 animals.

Results:

i. 0·03 *per cent in buffered isotonic saline*: The effects were inconstant. In some the reaction was mild: at the site of exposure there was focal hæmorrhage together with slight leucocytic infiltration of the leptomeninges and marginal glia; the superficial neurones alone showed degenerative changes leading in a few foci to necrosis (*Fig.* 297). The puncture wound in the right cerebrum was marked by a sharply defined area of coagulative necrosis bordered by hæmorrhage. In other instances the reaction was severe: the exposed cerebrum was often grossly herniated and had undergone a diffuse hæmorrhagic necrosis (*Fig.* 298) which sometimes extended to the wall of the lateral ventricle. In one instance there was intraventricular hæmorrhage and the necrosis extended to the hippocampus where it formed the opposing wall of the ventricle.

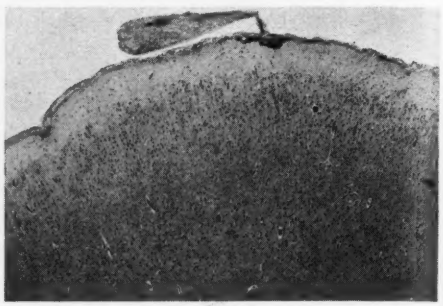

FIG. 297.—Showing effects two days after application of 0·03 per cent azochloramid in buffered isotonic saline (*p*H 7·4). Note slight leptomeningeal hæmorrhage and good preservation of cortex. (H. & E.). (× 19.)

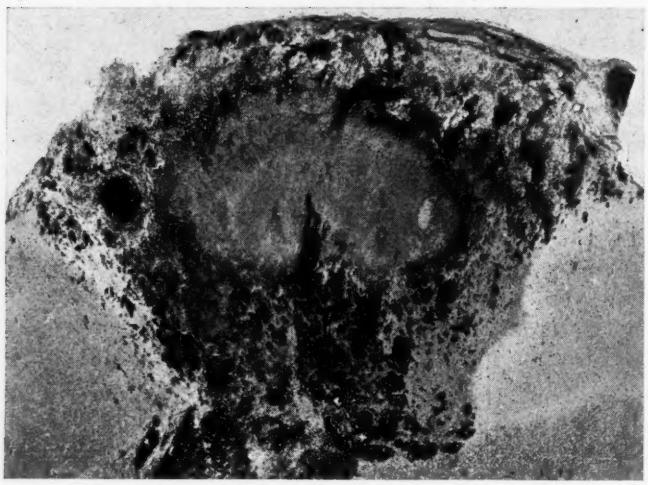

FIG. 298.—Intense hæmorrhage and necrosis two days after injection of 0·03 per cent azochloramid in buffered isotonic saline (*p*H 7·4). (H. & E.) (× 13.)

ii. 0·2 *per cent in triacetin*: The exposed area of brain was flat or slightly retracted; the leptomeninges contained a little diffuse hæmorrhage accompanied by leucocytic infiltration. In two animals cortical change at the site of exposure

was restricted to the superficial layers where the neurones showed severe degeneration; in the third a large circumscribed area of necrosis occupied the whole depth of the cortex. The injection into the right cerebrum resulted in a large oval area of coagulative necrosis surrounding the puncture wound. In one the solution had penetrated the leptomeninges over the dorsolateral border of the right cerebrum and had caused an intense fibrinoid necrosis in the subjacent cortex (*Fig.* 299).

COMMENT.—We can offer no explanation of the variable effect upon the brain of the saline solution of azochloramid. In the instances in which the reaction was severe the operations were done on four days, and for each of three days a fresh solution was prepared from tablets of the same sample as that used for those in which the reaction was mild. A solution nine days old was deliberately used on the fourth

FIG. 299.—Hæmorrhage and necrosis at dorsolateral border of right cerebrum one day after injection of 0·2 per cent azochloramid in triacetin. (H. & E.) (× 14.)

day for one animal. The distilled water used in preparing the solutions came from the same source. The saline used in irrigating the operation field was consistently isotonic. Portions of tissue from one of the animals severely affected were sterile on anaerobic and aerobic culture. In certain examples where the reaction had been mild the solution used had been kept for several days. But this evidently had no bearing on the intensity of the reaction because when later we deliberately used a stale solution the effects were of maximal severity. Finally, we are unwilling to ascribe the results to faulty technique: most of the severe results were obtained at a stage when we had obtained considerable operative experience and were using a standardized procedure.

The effects of triacetin solutions of azochloramid upon the brain differ from those of the saline solutions in that there is little swelling of the tissues even though considerable areas of necrosis may be present. The damaging effect of the solution was clearly seen in the massive necrosis caused by the injection into the right cerebrum: a similar necrosis was seen on the left side in one animal. The relative absence of cortical damage on the left side in the other two animals was probably due to defective penetration of the antiseptic.

b. **Eusol.**—The solution used was composed of chlorinated lime, 1 part; boric acid, 1 part; distilled water, 64 parts. The *p*H of the solution was about 9. It was injected into the cortex and applied to the surface of the cerebrum in 4 animals.

Results: In all except one animal eusol produced a considerable area of complete necrosis wherever it came into contact with the brain (*Fig.* 300). In the exception the mildness of the effects seen upon the left side may have been due to defective penetration of the solution; in the same animal severe necrosis was produced in the right cerebrum by the injection. Considerable œdema was found in the neighbourhood of the lesions, so much so that we chose this means of guaranteeing the formation of a hernia for our control observations. The destructive effect of eusol upon the ependyma and choroid plexus were clearly demonstrated

FIG. 300.—Intense hæmorrhage and necrosis extending to left lateral ventricle two days after application and injection of eusol. (H. & E.) (× 9.)

in one animal, in which the ependyma was stripped from the walls of the right ventricle and was necrotic. The choroid plexus of the ventricle was also necrotic.

Summary.—Severe necrosis attends the application to the brain of all solutions tested in this group. The solution of azochloramid in isotonic buffered saline produces inconstant effects: in some instances the reaction was little different from that obtained with normal saline, but in many others the damage was as great as that resulting from acriflavine. We were unable to account for this inconsistency.

4. ORGANIC MERCURIAL COMPOUNDS

a. **Metaphen (4-nitro-5-hydroxy-mercuri-ortho-cresol).**—We tested this substance in two concentrations, prepared from a stock 0·2 per cent aqueous solution supplied by the Abbott Laboratories: (i) 0·1 per cent in buffered isotonic saline (*p*H 10), 2 rabbits; (ii) 0·04 per cent in buffered isotonic saline (*p*H 10), 2 rabbits. The stock solution had a *p*H of 11 and reduction below *p*H 10 caused precipitation. In our solutions we used a sodium–hydroxide–boric–acid buffer.

Results: Hæmorrhagico-fibrinoid necrosis involved the leptomeninges at the site of exposure, spreading downwards through the cortex and subjacent white matter (*Fig.* 301). Hæmorrhage was conspicuous in more peripheral areas which

FIG. 301.—Hæmorrhage and necrosis of cortex two days after application and injection of 0·04 per cent metaphen in buffered isotonic saline (*p*H 10). (H. & E.) (× 13.)

had not undergone necrosis. The red corpuscles were often laked. The reaction was not appreciably milder where the weaker solution had been used.

b. **Merthiolate (sodium-ethyl mercuric thiosulphate).**—We tested this substance in two concentrations: (i) 0·1 per cent in buffered isotonic saline (*p*H 10),

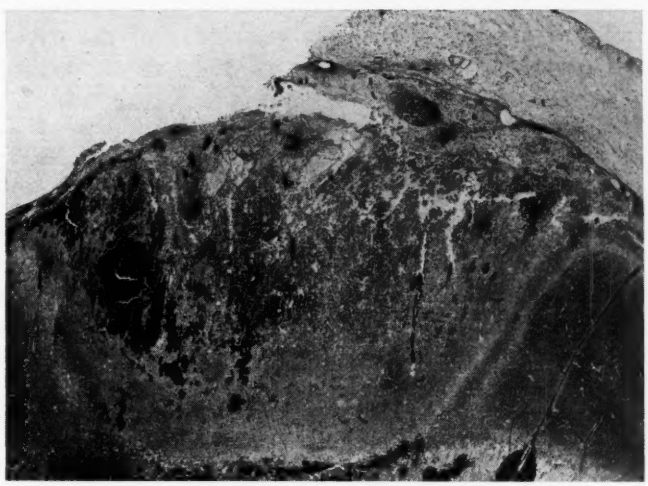

FIG. 302.—Hæmorrhage and necrosis two days after application of 0·1 per cent merthiolate in buffered isotonic saline. (H. & E.) (× 13.)

a stock solution supplied by Eli Lilly Co., 2 rabbits; (ii) 0·04 per cent in buffered isotonic saline (*p*H 10), made by diluting the stock solution with isotonic saline, 2 rabbits. As with metaphen, neutralization of the solutions to a point below *p*H 10 caused precipitation.

Results: With solution (i) there was severe fibrino-hæmorrhagic necrosis of the leptomeninges at the site of exposure, extending into the cortex about the puncture wound and forming elsewhere a wide saucer-shaped area reaching to the deepest layers of the cortex (*Fig.* 302). A zone of recent hæmorrhage and œdema was present about these necrotic areas; the red corpuscles were often laked.

A milder reaction was obtained with solution (ii). The exposed leptomeninges were occupied by a variable amount of hæmorrhage and leucocytic infiltration. A few hæmorrhages were present in the marginal glia and at the site of injection. An area of necrosis was found in the cortex at the apex of the puncture wound in one animal only. In both there was considerable œdema of the cortex, and stages of degeneration, but no necrosis, affected the superficial neurones throughout the exposed area.

c. **Phenyl Mercury Nitrate.**—A dry sample was obtained from British Drug Houses. We tested it in two concentrations: (i) a saturated (0·08 per cent) solution in isotonic saline (*p*H 10), 2 rabbits; (ii) 0·04 per cent in isotonic saline (*p*H 10), 2 rabbits. Solutions were difficult to prepare owing to the relative insolubility of the substance. It was impossible to neutralize the saturated solution and hence we used an unbuffered solution. A saturated aqueous solution had a *p*H of 4, but the saturated solution in isotonic saline had a *p*H of 10.

Results: With solution (i) the exposed leptomeninges underwent a severe fibrino-hæmorrhagic necrosis. There was no massive necrosis of the adjacent cortex, but hæmorrhages were abundant, especially in the superficial layers, where stages of degeneration leading to necrosis were conspicuous amongst the neurones. In many places the red corpuscles were laked. The puncture wounds, which were made in the exposed area in the left cerebral hemisphere, were not identified.

With solution (ii) the histological effects were similar, but were of milder degree. There was necrosis of the cortex immediately around the puncture wounds. Hæmorrhage was less conspicuous in the remainder of the exposed cortex and laking of the red corpuscles was slight and confined to one animal.

Summary.—The three organic mercury compounds tested are remarkably similar in their effects upon the brain. Concentrations of 0·1 per cent cause severe hæmorrhage and necrosis both of the leptomeninges and of the cortex at points of contact. There is a tendency towards the laking of blood in all three. In view of the considerable extent of the damage the slight degree of œdema is remarkable. When diluted to a concentration of 0·04 per cent the effects differ. Thus metaphen causes an amount of hæmorrhage that falls little short of that observed with the stronger solution. On the other hand, the results obtained with the weaker solutions of merthiolate and of phenyl mercury nitrate constitute an improvement. In both there was little destruction of tissue about the puncture wound; the surface effects were limited to the leptomeninges and the superficial neurones, the latter rarely being severely affected.

5. HYDROGEN PEROXIDE

Two solutions were investigated: (i) A stock 3 per cent aqueous solution obtained from British Drug Houses, equivalent to 10 volumes of available oxygen, was used in 2 rabbits—its *p*H was 4; (ii) A 3 per cent solution in isotonic saline buffered to *p*H 7·4, prepared from a stock 30 per cent aqueous solution, was used in 3 rabbits. There was great frothing of the solutions during application, followed

by marked injection of the surface of the brain. The operation area was well flushed with saline before closing the wound.

Results: Both solutions caused variable, but generally extensive, leptomeningeal hæmorrhage accompanied by marked hæmorrhage into and fragmentation of the cortex at the site of injection. The fragmented tissue was partly or wholly necrotic. There was severe œdema of the tissues surrounding the hæmorrhages, and the included neurones showed stages of degeneration leading to necrosis. Numerous small hæmorrhages and considerable fragmentation of the marginal glia were found throughout the exposed areas, accompanied by œdema and degeneration of the superficial neurones (*Fig.* 303). It seems probable that these changes were produced mechanically through excessive frothing of the solution, producing local emphysema of the tissues. We were surprised to find that this reaction was confined to the superficial tissues in view of the violence of the frothing at operation. The effects were greatly in excess of any that can be attributed to the acidity of the commercial solution. Moreover, we could not establish that neutralization of this solution caused any appreciable improvement in the histological results.

FIG. 303.—Fragmentation and hæmorrhage in superficial cortex two days after application of 3 per cent aqueous solution of hydrogen peroxide. (H. & E.) (× 19.)

6. SOLUSEPTASINE

Ampoules containing a 10 per cent solution of soluseptasine were provided by Messrs. May & Baker. The *p*H of this solution was found to be 10. Two dilutions were prepared: (i) 3·3 per cent in isotonic saline (*p*H 10), used in 2 rabbits; (ii) 3·3 per cent in buffered isotonic saline (*p*H 7·4), used in 2 rabbits.

Results: Small foci of diffuse hæmorrhage accompanied by sparse leucocytic infiltration were found in the leptomeninges. A few hæmorrhages were present in the superficial layers of the cortex and the site of the puncture wound. In one example injection of the unbuffered solution had caused a broad wedge of necrosis bordered by hæmorrhages in the upper three-fourths of the cortex. In the remaining examples the reaction to the injection was slight, consisting of a narrow zone of œdematous tissue in which a few leucocytes and degenerating neurones were present (*Fig.* 304). Apart from the puncture wounds the exposed cortex showed little alteration except for atrophy and hyperchromatosis of the superficial neurones.

FIG. 304.—Focal hæmorrhage and œdema two days after injection of 3·3 per cent soluseptasine in buffered isotonic saline (*p*H 7·4). (H. & E.) (× 19.)

With the exception of one animal, therefore, the effects of soluseptasine were little different from those obtained when normal saline was used. Although the

experiments are too few to warrant a definite conclusion, it appeared that the neutral solution excited rather less reaction than the unbuffered solution.

DISCUSSION

The summaries of our experiments provide some account of the histological effects of various antiseptics upon the brain of the rabbit. Our aim has been to find out which of the antiseptics of acknowledged germicidal power is least harmful to nervous tissue. The ideal antiseptic for the treatment of potentially infected wounds should destroy the bacteria but not the tissues.

Our operative procedures, apart from the antiseptic solutions tested, inflicted a certain amount of damage to the brain and leptomeninges. We estimated such damage in our preliminary experiments and found that the changes which resulted in the cortex and leptomeninges were relatively slight. Similar slight changes were found in simple cerebral hernias, but, when herniation was pronounced, superficial areas of necrosis were apt to occur through pressure of the cortex against the margin of the bone.

In addition we found it necessary to assess the damage inflicted upon the brain through deviation from normal of the antiseptic solution in respect of hydrogen-ion concentration and osmotic pressure. Under the conditions of our experiments alterations in *p*H as diverse as 2·2 and 10 caused surprisingly little additional degeneration. On the other hand, we found evidence that gross hypotonicity was responsible for severe damage to the brain. Our experiments with distilled water, for example, and with antiseptics diluted with distilled water, such as dettol, resulted in extensive necrosis and hæmorrhage in the exposed brain.

Isotonicity, therefore, is an important requisite of any solution that is brought into contact with the brain. We do not hesitate to stress this elementary biochemical consideration, for it is frequently ignored in the antiseptic treatment of wounds. As far as we are aware, there is no difficulty in achieving isotonicity when an antiseptic is prepared in watery solution. Moreover, a certain amount of latitude is almost certainly permissible. Thus Willmer (1927) found that cultures of heart muscle were not immediately killed by sodium chloride concentrations of 0·2 and 1·2 per cent.

The establishment of neutrality is less simple. Not all antiseptics can be prepared in a neutral solution. Some, like the acridine compounds, give acidic solutions which form precipitates on neutralization; others, like the organic mercury compounds and the xylenol emulsions, are only stable in an alkaline solution. There is, however, some evidence that strict neutrality is not essential in a fluid which is to be brought in contact with living tissues for a short period only. Our own experiments, though limited, suggest that fluids at a *p*H of 2·2 and 10 respectively are not grossly destructive when applied for a period of ten minutes. Lewis and Felton (1922) found that the tissues of the 9-day chick embryo would actually grow in cultures having a *p*H varying from 5·5 to 9; the optimum was between 6·8 and 7. Fischer (1930) reports that survival of chick fibroblasts without growth is possible at *p*H 4·8. Allowing for the probability that the cells of the chick embryo are more adaptable than those of the adult brain, it may be conceded that the range of *p*H permissible for fluids that are in contact with the brain for a short period lies, at a cautious estimate, between 6 and 8·5. Further investigation might show that the range is even wider.

It is also necessary to consider whether the germicidal properties of antiseptics are likely to be impaired by adjustment of their watery solutions in respect of osmotic pressure and hydrogen-ion concentration. We have no information that the germicidal effects of antiseptics are altered through rendering their solutions isotonic, except in so far as there is a tendency on the part of physiological saline to increase the colloidal state of certain of the antiseptic dyes at the expense of the crystalloid portion, thereby depressing their germicidal activity (Hirschfelder and Wright, 1929). Precise information is, however, not available on this point.

On the other hand, it is well known that the germicidal power of some antiseptics varies with the *p*H of their solutions (von Oettingen, 1932). Browning, Gulbransen, and Kennaway (1919) showed that the germicidal titre of acriflavine increases with increased alkalinity, whereas the reverse is true of perchloride of mercury. They found that the germicidal titre of acriflavine against *Bacillus coli* in peptone water was 100 times greater at *p*H 11 than at *p*H 4 to 5. It is of practical importance that the addition of sodium or potassium salts, or of phosphates, which may be used in buffering, does not alter the germicidal activity either of acriflavine or of proflavine (Eggerth, 1926).

With antiseptics of the dettol and supersan type, reduction of the *p*H towards the neutral point causes an alteration in the stability of the emulsion and oily droplets tend to separate. We do not know whether these droplets represent the active principle or the essential oils by which the active principle is held in solution. Any separation of the active principle presumably causes a proportionate decrease in germicidal activity.

The antiseptic solutions tested by us upon the rabbit's brain have mostly been extraordinarily destructive. Two groups, however, deserve special consideration :—

1. Two members of the acridine group, proflavine sulphate and 2 : 7 diaminoacridine hydrochloride, caused a degree of damage that we would consider minimal. Thus the application of a 0·1 per cent isotonic and buffered solution of proflavine produced effects similar to those seen when isotonic saline alone was used. These effects were in marked contrast to those observed after the application either of acriflavine or of euflavine. This surprising result was not anticipated, as such variations have not previously been reported. We are unable to explain this divergence in behaviour on the part of closely related compounds. It may, however, be significant that neither acriflavine nor euflavine are pure substances. Gailliot (1934) and others have pointed out that acriflavine (B.P.) is not, as described, " the hydrochloride of 2 : 8 diamino-10-methyl acridinium chloride ", but consists of a mixture of this compound with approximately an equal quantity of diaminoacridine-hydrochloride. On the other hand, both proflavine sulphate and 2 : 7-diaminoacridine hydrochloride are chemically pure substances. Their germicidal potency is of the same order as that of acriflavine (Albert et al., 1938). An analysis of the observations of Albert and his associates shows that the biological properties of the various acridine compounds vary unaccountably. Thus on subcutaneous injection the lethal dose for mice per kg. of body-weight is 0·05 g. for acriflavine, 0·2 g. for proflavine, and 0·5 g. for 2 : 7-diaminoacridine hydrochloride, while the maximum concentration of the antiseptic which permits motility of human leucocytes is about the same for all three. In contrast to these observations a higher percentage of staphylococci is phagocytosed when proflavine is present in a concentration of 1 in 1000 than when 2 : 7-diamino-acridine hydrochloride is present

in the same concentration. From this it may be deduced that tests of toxicity in terms of lethal subcutaneous doses bear no relation to the effects which may be produced directly upon cells.

In supporting proflavine sulphate (0·1 per cent) as an antiseptic suitable for prophylactic application to cerebral wounds, we are influenced by the following additional considerations :—

a. It can be readily prepared in isotonic solution buffered to *p*H 6·2.

b. When tested *in vitro* its bactericidal properties, in common with acriflavine and euflavine, have been well established (Browning and associates, 1917 ; Eggerth, 1926 ; Garrod and Keynes, 1937).

c. Chemotherapeutic tests in animals have shown that these compounds are able to sterilize experimental wounds which have been recently infected with virulent organisms (Neufeld, 1922 ; Schiemann and Wreschner, 1922 ; Browning, 1934).

d. It is effective in the presence of serum. Claims that proflavine and acriflavine are actually more potent in serum have been disputed. In this connexion the suggestion of Eggerth (1926) that observations in support of this claim are attributable to the increasing alkalinity of serum on standing is of interest.

e. Observations of the effects of various antiseptics upon tissue cultures *in vitro* have indicated the comparatively mild effects exerted by proflavine and acriflavine (Mueller, 1919 ; German, 1929).

f. The histological appearances seen in our preparations did not suggest that the application of proflavine caused any alteration in the normal processes of inflammatory reaction and healing. However, in view of reports accumulated during the last war of delay in healing following prolonged exposure to flavine, we suggest that a single application only should be given in the earliest stages of treatment.

g. The recent investigations of Manifold (1940) upon the inhibition of brain respiration by various antiseptics have shown that, with the exception of 2 : 7-diaminoacridine, proflavine sulphate is the least toxic of those which we have tested.

2. *The chlor-xylenol compounds*, such as dettol and supersan, in 5 per cent isotonic buffered solutions, caused relatively little damage to the brain, although substantially more than proflavine. Their application, however, has so far been confined mainly to midwifery, where they have proved their value in sterilizing the skin. Very little is known of their action upon bacteria in open wounds. Colebrook and Maxted (1933) state that a 2 per cent solution of dettol will kill *Streptococcus pyogenes* and *Bacillus coli* within two minutes even in the presence of pus, but that there is no appreciable action when the bacteria are incorporated in fragments of blood-clot. In the present state of our knowledge, therefore, the use of these antiseptics for brain wounds cannot be recommended.

Still less can the remaining antiseptics on our list be advocated. The saline solution of *azochloramid*, alone of the halogen group, appeared to have much in its favour, and, in certain of our experiments, the results were fully as good as those obtained with proflavine. But our inability to obtain consistent results in spite of every precaution has undermined our confidence in this antiseptic. Both azochloramid in triacetin and eusol are condemned on account of their highly damaging effects.

Of the organic mercurial compounds, *merthiolate*, in a concentration of 0·04 per cent, appeared to be least destructive. The highly germicidal powers claimed for it by Powell and Jamieson (1931) were, however, not confirmed by Colebrook and

Maxted (1933). Its solutions, which are strongly alkaline, cannot be neutralized on account of precipitation. Its bactericidal activity in open wounds has not been proved, though its efficiency *in vitro* is only slightly reduced by the presence of serum. Hence the value of merthiolate in this sphere has not yet been fully established. The same is true of *phenyl mercury nitrate*.

Hydrogen peroxide, as already stated, cannot be claimed as an effective germicide in the treatment of wounds. It is widely used in neurosurgery as a cleansing and hæmostatic agent. Its popularity for these purposes should be modified by the consideration that it causes fragmentation with consequent hæmorrhage of the cerebral tissues with which it comes in contact. Its penetrative powers, however, are comparatively slight. We have not established that its damaging effects are appreciably lessened by rendering its solutions isotonic and neutral.

The *sulphanilamide compounds* deserve a special note. Their use as local antiseptics in contradistinction to systemic action has been disparaged (Buttle, 1937; Browning, 1939). Nevertheless Jensen, Johnsrud, and Nelson (1939) report favourable results in a series of 41 cases of compound fractures and dislocations in which at operation they applied crystalline sulphanilamide to the bone ends besides carrying out the ordinary surgical measures of débridement, reduction, primary suture, and immobilization. Two only of their cases became infected. Corroborative evidence of the efficacy of the local application of sulphanilamide was provided by a series of experiments on guinea-pigs in which the ribs were fractured and contaminated with *Staphylococcus aureus hæmolyticus*. Most of the animals treated by local application of sulphanilamide in addition to suture of the wound healed promptly, while most of the animals not treated with sulphanilamide, or treated only by the systemic administration of sulphanilamide, developed severe osteomyelitis.

We investigated the local effects produced by soluseptasine, which appears to be one of the more soluble of the sulphanilamide compounds. It can be buffered to normal *p*H, and, in our hands, concentrations of 3·3 per cent produced little inflammation or degeneration in the brain and leptomeninges. These results are in agreement with the observations of Wolff and Julius (1939) upon the effects of various concentrations of sulphanilamide on cultures of chick fibroblasts. They found that the growth and morphological appearances of the cultures were unimpaired in concentrations up to 0·1 per cent. There was no definite deterioration until a concentration of 0·3 per cent was attained. We have no information concerning the histological effects produced by the intrathecal injection of soluseptasine and do not advocate this form of therapy until experiments have proved it to be harmless. On the other hand, there appears to be no reason why recently inflicted wounds of the cerebral convexity should not be treated with soluseptasine or other soluble sulphanilamide compounds if future work confirms their efficacy in controlling local infections by this means.*

CONCLUSIONS

The histological effects of various antiseptic solutions upon the brain of the rabbit have been recorded.

Reasons have been given why such solutions should be isotonic and as far as possible buffered to neutral point.

* Since this paper was submitted for publication we have similarly tested both sulphanilamide and sulphapyridine in powder form. Using small quantities we have found that these substances inflict no appreciable damage upon the brain (*Lancet*, 1940, **2**, 100).

Proflavine sulphate in 0·1 per cent isotonic solution buffered to *p*H 6·2 is not substantially more injurious to the brain than normal saline, and is, on this and more general grounds, the antiseptic to be preferred for the prophylactic treatment of brain wounds.

2 : 7-diamino-acridine hydrochloride is similar to proflavine in its action; its effect upon the tissues deserves further investigation in view of its low toxicity.

Most of the other antiseptic solutions tested were highly destructive. Certain exceptions have been discussed, but, in the absence of bacteriological proof of their germicidal potency in open wounds, their use is not at present recommended. In no instance has their action upon the tissues indicated any superiority over proflavine sulphate.

We are greatly indebted to Professor W. E. Le Gros Clark for allowing us to make our experiments in the Department of Human Anatomy, Oxford, and to Mr. J. O'Brien for his help in preparing the solutions. Our thanks are also due to Professor Hugh Cairns for his help in the presentation of this paper, to Professor J. H. Burn and Dr. W. Linnell for their interest and advice, and to the manufacturers mentioned in the text for their courtesy in providing the chemicals.

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SHORT NOTES OF RARE OR OBSCURE CASES

AN UNUSUAL FATALITY FROM URÆMIA

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Cases of congenital polycystic disease of the kidneys are of rare occurrence in the individual practice of one observer; directly the diagnosis has been established, the question of prognosis arises. The condition ultimately is invariably fatal, but it is compatible with surprisingly long periods of survival in many instances, until, as in the case herewith recorded, the onset of a fatal uræmia may be evoked by an apparently trivial incident.

CASE REPORT

On April 24, 1939, a man of 54 years, a vanman by occupation, was admitted to St. Vincent's Hospital, Dublin, with signs of a recently inflicted injury to his left shoulder-joint. He displayed no evidence of shock, had not been unconscious, and gave a clear account of the accident in which the injury had been sustained. Briefly, this was to the effect that as the result of a collision with a motor-lorry he had been thrown from his driving-seat into a field, his fall being broken by a high hedge, but for which his injuries might have been of a more extensive nature.

On Examination.—He presented a diffuse tender swelling beneath the deltoid muscle, with inability to carry out any movement at the shoulder without pain. X-ray examination disclosed no sign of fracture. The extent of his injuries seemed to be a subdeltoid hæmatoma, with some bruising of the periarticular tissues.

Progress.—The next afternoon I was again called to see him. He was now deeply unconscious and could not be awakened. To my inquiry as to the manner of onset of his unconscious state the sister-in-charge reported that shortly after taking a feeder of soup about 11 a.m., he had announced his intention of "having a snooze". No particular notice of a sleeping patient was taken until it became necessary to rouse him for his dinner; the nurse who brought him his dinner had not been able to rouse him; she had elevated his eyelids and found his pupils equal and reacting to light. Some slight twitchings were then observed in his right arm and leg, but none in the muscles of the face. His temperature was 97·6° F., pulse-rate 76, and respirations 18 to the minute.

He was breathing quite easily, with no trace of stridor. There was no flaccidity of the limbs as we lifted them; examination of knee-jerks, Babinski, and ankle clonus was not very satisfactory. The cerebrospinal fluid on lumbar puncture was quite clear.

My house surgeon reported that a specimen of urine, examined that morning as routine, had contained some albumin. A catheter specimen was taken for the laboratory, and a specimen of blood withdrawn for blood-urea estimation.

At 6 p.m. that afternoon (24 hours after admission) his condition was unchanged. A catheter, passed at 6.30 p.m., drew off 38 oz. of clear urine. The report on the specimen sent to the laboratory earlier in the day was as follows: "Reaction acid. Sp. G. 1010. Albumin + 2. Sugar absent. Very little deposit on centrifuge: a few leucocytes, no red blood-cells, an occasional epithelial cell, and some amorphous deposit." The blood-urea was 79 mg. per 100 c.c. blood.

Next morning, his temperature was 103° F., pulse 116, respirations 20. All day he remained unconscious, with very short intermissions. No change was observed in the pupils. Occasional twitchings were noted in the right arm and both legs. A catheter, passed at 2.30 p.m., withdrew only 7 oz. of urine. His family, who were grouped around him, he entirely failed to recognize. His eldest son, a man of some 30 years, assured me that his

father " had never been a day sick in his life ". None of the family then present, apparently, had ever known him to complain.

He died in coma on the third day after admission and, so far as we could ascertain, some 80 hours after the accident.

Death was clearly due to an acute uræmia. The onset of the uræmic state had followed on the reception of a not very severe injury. What connexion, if any, was there between the injury and the uræmia ?

POST-MORTEM EXAMINATION.—The injured shoulder disclosed marked bruising and laceration of the deltoid muscle and subdeltoid bursa. There was no fracture, nor any sign of intracranial injury. As we opened the abdomen our attention was drawn to the presence of three small cysts on the inferior free edge of the liver ; these contained no hæmorrhages, nor had they the appearance of trauma. Both kidneys were grossly enlarged and nodular as one palpated them through their peritoneal coverings. Once removed from the body, it was seen that both were the seat of advanced polycystic disease of the so-called congenital type.

DISCUSSION

In estimating the actual cause of this man's death, it would seem that the absorption of the extravasated proteins from the blood in the hæmatoma and torn muscle, and their subsequent excretion by the kidneys, was too great a physiological strain for these organs which had hitherto responded without protest to the various strains which an active outdoor life had laid upon them.

The basic condition in this case was that of congenital polycystic disease of both kidneys. The condition present at birth undoubtedly is of a progressive nature. It almost always affects both kidneys and is invariably fatal, but its course may extend over many years.

As to its incidence, Thomson Walker has recorded that out of 389,773 admissions to the London Hospital in the years 1900–24 only 79 cases were found clinically (i.e., 1 in 4933).

As to the cause of death in polycystic disease, slightly more than half the recorded cases have died of a terminal uræmia. Sieber[2] found that out of 98 instances in which post-mortem investigations had been made, uræmia was the lethal factor in 50 cases.

The expectation of life is difficult to assess with any accuracy. Josseraud[1] has recorded the ages at death of 187 patients with polycystic disease of the kidneys as under :—

10–20	years	2	cases
20–30	,,	13	,,
30–40	,,	26	,,
40–50	,,	69	,,
50–60	,,	47	,,
60–70	,,	17	,,
70–80	,,	11	,,
80–90	,,	2	,,

In this list of collected cases 30 patients out of 187 survived the 60th year. Sieber[2] has collected 244 cases, with the undermentioned age groups at death :—

0–20	years	32	cases
20–30	,,	26	,,
30–40	,,	22	,,
40–50	,,	67	,,
50–60	,,	40	,,
60–70	,,	10	,,
70–80	,,	6	,,
80–90	,,	2	,,

In this list, only 18 out of 244 patients survived the 60th year.

Some months after his death, I learned a few relevant details of the previous personal history of my quondam patient. Prior to becoming a vanman, he had been a member of the Dublin Metropolitan Police, and on taking up civilian employment was in receipt of a small pension from this source. He had been seven years in civil employ, during which period his time-sheet showed that he had never lost one single day's work through illness. From his service file as a policeman one learned that some years earlier he had been in hospital for a period of four weeks, when his ailment had been certified from the hospital as " lumbago ". Is it probable or improbable that this spell of lumbar pain may have been caused by a temporary increase of tension within the cysts?

He had his life insured for a small sum. Here again, the congenital lesion would appear to have given rise to no signs or symptoms likely to have caused a rejection of his application for a policy.

Cases of polycystic disease of the kidney would seem to present themselves under two main types: (1) The ' congenital ' type, in which the subjects are either stillborn or die within one year of birth (roughly 30 per cent of recorded cases); and (2) An ' adult ' group, in which symptoms do not appear till after the twentieth year, and in which the renal failure progresses slowly, with surprisingly long periods of survival (roughly 65 per cent). Both types are now regarded as different manifestations of the one pathological entity.

The observation is frequently recorded in the literature that a patient with scarcely any normal renal tissue may yet enjoy good health for several decades until, comparatively suddenly, at the age of forty or upwards, the condition will manifest itself and the patient speedily die of uræmia. The wonder in the case above recorded is, not that the patient should have died from a trivial accident in middle life, but that he should have survived so long with so little renal tissue and without symptoms.

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ANEURYSM OF THE CŒLIAC ARTERY

BY A. DAVID LEVAY

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CASE REPORT

THE patient, a widow of 58, was first seen forty-eight hours after the onset of severe abdominal pain, colicky in type, felt mainly in the epigastrium and radiating to the right back and shoulder. There had been nausea, but no vomiting or constipation, and she noticed yellowness of the skin on the day of admission.

An attack of a similar type six months before had been initially diagnosed elsewhere as appendicitis, but the right kidney was later explored and said to have been removed. There had been no symptoms whatever in the interval. Fifteen years previously hæmatemesis had been thought to be due to a gastric ulcer, but symptoms soon ceased.

ON EXAMINATION.—The patient gave a complete picture of acute cholecystitis with regional peritonitis. She was acutely ill, slightly jaundiced, with a temperature of 99° soon

rising to 102°, and a pulse-rate of 110. The epigastrium was immobile and there was a diffuse swelling in the right hypochondrium, with more extensive rigidity extending to the loin laterally and the midline medially. Marked tenderness and slight œdema were present over this area. On deep palpation there was the sensation of a smaller underlying mass in the right hypochondrium.

TREATMENT.—She was treated expectantly, in the Fowler position, with atropine, magnesium sulphate, hot applications, and glucose drinks, and next day was very much better. The pulse-rate had fallen to 90, much of the rigidity and tenderness had disappeared, and a definite mass was palpable in the right upper abdomen extending up under the costal margin, but not moving on respiration. This was considered to be a mucocele or empyema of the gall-bladder. The following day the patient began to fibrillate rapidly, developing basal pulmonary consolidation but maintaining her general state well, and she died very suddenly four days after admission in circumstances suggesting pulmonary embolism.

POST-MORTEM EXAMINATION.—The body was that of a well-nourished elderly woman with an operation scar in the right loin. The lungs showed recent infarction of both lower lobes. The pulmonary artery contained ante-mortem clot in either main branch, while the heart was normal except for slight calcification of the aortic orifice and a common origin for both coronary arteries. On opening the abdomen the stomach was displaced downwards and the lesser omentum bulged forward by a tense bloody effusion in the lesser sac. The latter was opened and the pancreas found, contrary to expectation, to be normal and also displaced downwards. Masses of blood-clot of recent formation filled the lesser sac and extended widely in the retroperitoneal space, and the spherical sac of a large aneurysm occupied the gap between the aortic orifice and the upper border of the pancreas. Both kidneys were present. The stomach was normal. The gall-bladder contained two cholesterol stones, but was not infected. The whole of the tissues of the posterior abdominal wall was removed *en bloc* and dissected. This revealed that the cœliac axis immediately after its origin from the aorta expanded into a spherical sac some three or four inches in diameter. The wall of the sac had only a thin lining of laminated clot and was breached anteriorly in several areas. Blood and blood-clot filled the lesser sac, though none had reached the peritoneal cavity, and extensive recent retroperitoneal hæmorrhage had occurred extending on both sides of the midline in front of the kidneys up to the diaphragm, and compressing the inferior vena cava, the lumen of which was largely occluded by recent thrombus, the undoubted source of the embolus. The postero-superior sac wall was firmly adherent to the diaphragm. The left gastric, splenic, and hepatic arteries originated from the base of the sac eccentrically and were patent. The liver and spleen showed remarkably little sign of venous congestion. There was no sign of syphilis, general or aortic, and very little atheroma.

Comment.—This case was interesting, apart from its rarity, by reason of the close simulation of acute cholecystitis, the recovery from an extensive rupture of such a large aneurysm, and the causation of death by pulmonary embolus detached from the clot in the inferior vena cava. The shoulder pain and jaundice were due to pressure on the diaphragm and bile-ducts respectively. One was thankful to have decided against operation; the tense effusion in the lesser sac would have inevitably led to the diagnosis of hæmorrhagic pancreatitis and the results of attempted drainage can be imagined.

DISCUSSION

Aneurysm of the cœliac artery is one of the rarest of surgical conditions. Only two cases have been previously reported (Smith, 1927; Roós, 1929). Details of Smith's case only are obtainable and these are worth brief description. The patient was a boy of 16 with diffuse pulmonary tuberculosis associated with tuberculosis of the spleen, liver, pericardium, and cerebrum. He began to have subxiphoid pain a year before admission, and died suddenly after collapse while in hospital. He had much free peritoneal blood, with a sac the size of a golf ball above the head of the pancreas. This was a saccular aneurysm of the right wall of the vessel, which was otherwise unaffected, and the left gastric, splenic, and hepatic branches ran normally behind the sac. The mesenteric and cœliac

lymph-glands were caseous and the aneurysm wall was infiltrated in several places with tuberculosis. There was no evidence of syphilis in sections of the sac wall, or in any part of the body. Roós's case, too, was associated with generalized tuberculosis, which suggests a similar aetiology. Neither was diagnosed before autopsy. The only general conclusions which can be drawn from such a small number of cases are the natural failure of diagnosis before rupture, the absence of syphilis as an aetiological factor, and the rapid progress to rupture and grave or fatal hæmorrhage after the first symptoms of abdominal pain.

SUMMARY

A case of cœliac aneurysm is described of unknown aetiology in which rupture simulated acute cholecystitis. Only two other cases have been recorded, both associated with generalized tuberculosis.

I wish to thank Mr. H. W. S. Wright, Dr. J. N. O'Reilly, and Dr. S. Roodhouse Gloyne, for their help and advice.

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ALKALI POISONING IN A CASE OF GASTRIC ULCER

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WHEN one considers the number of cases of gastric ulceration which are probably receiving self-treatment by some form of 'stomach powder', it is remarkable how few are the cases of alkali poisoning that are received in hospital for treatment. From this point of view a short note on a case which recently came under my care may be of interest.

CASE REPORT

HISTORY.—The patient, W. H. U., a man aged 29, knew himself to be suffering from gastric ulcer, a condition which he had had for five years. He had been in the habit of dosing himself with 'stomach powders' to relieve the pain, but during the last three months matters had got worse. The pain was constant rather than related to food, and the powders which once relieved the pain now failed to do so. In consequence the dose was increased, so that latterly the patient was taking as many as twelve teaspoonful doses during the day and two during the night. As a result the vomiting got worse too. To allay these symptoms the patient then took an alkaline mixture containing bismuth, as well as his other medicine, adding alkali to alkali. At about this time his wife noticed in addition to his other troubles, a marked change coming over his mental outlook. He was depressed and irritable, at times she thought "delirious".

ON ADMISSION.—The patient complained of vague headache and was markedly drowsy. His face was flushed and the conjunctivæ injected. Shortly somnolence passed into coma and the same night the patient had a severe fit. The paroxysm lasted several minutes and involved the muscles of the upper and lower limbs in tetanic contractions. This was controlled by the administration of rectal paraldehyde, and later, in response to the administration of intravenous glucose salines there was a gradual improvement. Minor fits, however, occurred from time to time. There were attacks of hiccup and the patient had periods of

"mind wandering" and became strange in manner. On the whole, however, there was continued improvement, so that by December 20, 1938, fourteen days after admission, an X-ray examination was possible which confirmed the diagnosis of gastric ulcer (Dr. C. Hilliard). All this time a check was kept on the serum bicarbonate, which ranged round 70–80 vol. per cent (Dr. E. N. Allott), and the blood-urea, which fell from 159 mg. per 100 c.c. in the beginning to 44 mg., but then suddenly rose again towards the end to 182 mg. (Dr. A. B. Rosher). The serum chlorides were estimated at 242·4 mg. per cent. It is interesting to note that the gastric acidity as shown by the test-meal remained steady at normal levels. The urine was reported on as follows: "Hyaline casts present, some red blood-cells, and a slight excess of polymorphs. No organisms were seen in the direct film. Albumin—a small amount. Chlorides 0·308 per cent calculated as NaCl; *p*H 6·9." (Dr. E. Hardy.)

After a few days the gradual but steady improvement which the patient was making was interrupted by a severe attack of vomiting, copious in amount, differing in character from the previous attacks, and rather suggestive of pyloric obstruction. It had previously been decided to defer operation, but in view of this new development and despite the high blood-urea, operation was undertaken immediately.

OPERATION.—Under rectal paraldehyde and gas and oxygen inhalation anæsthesia (Dr. A. E. Palmer), the abdomen was opened and a quick gastro-enterostomy performed. A large ulcer was found in the pyloric region of the stomach extensively indurating its wall and constricting its lumen, but apparently simple in nature. The cardiac end was somewhat dilated, but otherwise healthy.

SUBSEQUENT PROGRESS.—The patient made an uninterrupted recovery from his operation and the improvement in his condition was immediate and remarkable. A final blood examination now gave the following figures: blood-urea 33 mg., serum bicarbonate 54 vol., and serum chloride 322 mg. The patient visited the hospital four months after his discharge and described himself as being "in perfect health" and glad to be back at work. To-day, twenty months after, he is doing a full day's work in the shipyards.

Comment.—Two clinical points are illustrated by this case:—

1. The condition may remain unrecognized for some time on account of the insidious nature of the onset of the symptoms, which resemble those of the original gastric ulcer.

2. The symptoms of mental deterioration which are often a characteristic feature of alkali poisoning were important in this case as it was not until they appeared that the patient sought admission to hospital.

INFECTIVE CUTANEOUS GANGRENE IN AN INFANT

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EXTENSIVE and rapidly progressive ulceration in an infant provides an arresting clinical picture which cannot fail to arouse interest. Such a condition appears to be of the greatest rarity. In describing the case attention is drawn to interesting points in the pathology and treatment.

CASE REPORT

Brenda Taylor, a girl aged 3 weeks, was first seen in the Out-patients' Department in January, 1940.

In the natal cleft, posterior to the anus, was a narrow ulcer about $\frac{3}{4}$ in. long and $\frac{1}{8}$ in. wide, apparently formed in a crack in the skin. Dr. Pritchett, of Knaphill, wrote to say that a sore place had been noticed for about a week and that it was growing larger. Little discharge was seen, and the edges were slightly œdematous and swollen. It was thought

possible that the ulcer was a syphilitic manifestation, and a Wassermann reaction of the mother was taken, which proved to be negative. Lotio nigra was prescribed and the child was sent home. Next week the weather was very bad, and the child was not seen, but the mother reported that the ulcer was cleaner and seemed to be healing. A week later the mother telephoned again to say that the child was not getting on, and it was at once admitted to Woking Hospital.

After admission on February 7 the infant weighed 9 lb. 2 oz. The temperature was normal, and the child did not look ill. The ulcer was spreading over the left buttock, and was then rather larger than a postage stamp. It was first dressed with lotio nigra, and blood for a Wassermann reaction was taken. This proved to be negative like that of the mother. Nevertheless a course of weekly injections of stabilarsan was started (0·05 g. intramuscularly each dose). There was no improvement, but extension was slow. Various disinfectants were tried, including glycerin, alum and zinc lotion, flavine emulsion, brilliant-green paint, etc., and ultra-violet light exposures daily. Smears and cultures from the ulcer showed mixed organisms, chiefly *B. coli*, and no indication of a definite pathology.

Fig. 305.—Photograph showing the extent of the ulceration of the buttocks.

About Feb. 15 the ulceration began to spread with great rapidity. There was not much pus, but the tissues just dissolved away. M & B 693, ½ tablet daily, was given without any benefit. The baby still seemed content and not at all distressed, and on Feb. 16 the weight actually rose to 9 lb. 5 oz., but it fell away again to 9 lb. 2 oz. on Feb. 21. The alarming condition then present is shown in the photograph (*Fig.* 305). A large part of the skin of the buttock had disappeared and the fat was pitted and irregular. The edge of the ulcer showed slight œdema and the least possible red flush, but did not seem to be very tender.

The most drastic treatment was clearly required to check the spread of the ulceration. The ulcer was considered too extensive to excise entirely, and it was dealt with as follows: A strip about ¼ in. wide containing the growing edge was completely excised from one-third of the periphery, and the raw surface cauterized. For another third the skin was cut down to the fascia beyond the ulcer margin, and the incision cauterized to control hæmorrhage, without removing any tissue. The remaining circumference was simply cauterized deeply with a cautery knife beyond the ulcer margin. A simple dressing of flavine emulsion was applied. The child was little the worse for this interference, although the weight dropped ½ oz. during the next two days. The ultra-violet light exposures were continued. The ulcer ceased immediately to spread, and healing was obvious in about ten days. It appeared first and progressed most rapidly in that part of the wound in which the skin had been merely seared with the cautery knife. Healing progressed slowly all through March, and was not complete until April 5, when there was sound epithelial covering, but of course the loss of tissue remained. At this time the baby weighed 10 lb. 15 oz. and seemed remarkably well and a source of great pride to its parents.

A careful examination of the tissue excised from the growing edge of the ulcer was carried out by Professor Barnard. He reported as follows: "Chronic purulent ulcer of buttock and tissues over the sacrum. Staphylococci in the superficial part and streptococci in the depths."

Commentary.—The outstanding clinical feature of this case was the rapid extension of ulceration in the later stages. The ulcer scarcely changed in appearance for several weeks, but between Feb. 14 and Feb. 20 it spread with fearful rapidity and nearly doubled in size. There was little discharge, but the skin just melted away and the loss of tissue was most marked. In view of the relatively large ulcerated area, it was also astonishing to note the placid and contented appearance of the child, and the very slight loss of weight.

The fundamental pathology of this unusual condition appears to resemble that present in certain cases of extensive cutaneous ulceration in adults, which have been described by various authors, and particularly in this JOURNAL in a most comprehensive article by Stewart-Wallace.[1] These cases have usually arisen in the cut surface of the skin after operations for thoracic empyema, and particularly for appendix abscess and other septic conditions of the bowel. Several such cases fully investigated by Meleney[2] showed a double infection by staphylococci and streptococci, which appeared to be a specific cause of the gangrene. Cultures of these organisms caused gangrene when injected into guinea-pigs and rats, but only when both were present together. The writer has personal experience of three such cases, which are probably less rare than published records suggest, and the condition is now well recognized. In the case under discussion no operation wound was present, but we may probably assume a scratch of the skin or a crack produced by the chafing of a napkin. The situation of the ulcer behind the anus confirms the suggestion of a relation between such ulcers and the bowel. In this baby also, both staphylococci and streptococci were demonstrated by Professor Barnard in the tissue excised from the growing edge of the ulcer. The complete barrier to further spread provided by simple incision and cauterization was most dramatic evidence of the success of the treatment recommended by Stewart-Wallace in the paper referred to above, where also an extensive bibliography may be found.

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REVIEWS AND NOTICES OF BOOKS

Malignant Disease and its Treatment by Radium. By STANFORD CADE, F.R.C.S., Surgeon, Westminster Hospital, Mount Vernon Hospital, and The Radium Institute; Lecturer in Surgery, Westminster Hospital Medical School; Associate Examiner in Surgery, University of London; late Hunterian Professor and Arris and Gale Lecturer, Royal College of Surgeons of England; Member of the Grand Council, British Empire Cancer Campaign. $9\frac{7}{8} \times 6\frac{1}{2}$ in. Pp. 1280 + xi, with 623 illustrations, many in colour. 1940. Bristol: John Wright & Sons Ltd. 75s. net.

IT is comparatively recently that radium was discovered and its properties in the treatment of disease investigated, and now this book appears giving a very full account of the matter in its many aspects. The first-hand knowledge of the subject has been gained by the author from his experience in the treatment of 4000 cases of malignant disease during the years 1924 to 1939. But in addition to this personal experience he has given a very extensive presentation of the subject as derived from current literature, chiefly that of America, France, Scandinavia, and Germany, as well as of this country. Every one of the thirty chapters is followed by a list of references to articles in the literature bearing upon the subject of the chapter. This in itself constitutes a very valuable source of reference. The book is divided into three parts.

Part I (97 pages) deals with radio-activity, and in its compilation the author has been assisted by H. T. Flint, D.Sc., who writes on distance radiation by mass units, and by C. W. Wilson, Ph.D. (radium dosimetry) and L. H. Gray, Ph.D. (measurement of radium plaques). This part of the work in its five chapters deals with the essential facts of physics, and with the aid of various diagrams gives an account of a difficult subject which goes far to making it clear to the average medical reader. For example, the electroscopic detection of small quantities of radium by Chalmers's device known as the 'clucking hen' is simply described and illustrated. The estimation of dose in radium therapy has become a very important and complex subject, and the old days when this was expressed simply as the amount of radium multiplied by the hours of exposure are long past. In its place we are given a very complicated physical and mathematical formula for estimating the effective dose.

Part II (184 pages) deals with the effect of radiation on normal and malignant tissues. The effect of radium appears to be chiefly in modifying the cell nucleus and its mitotic activity. This goes some way to explaining the difference of sensibility of different tissues, primitive tissues and those undergoing rapid cell division such as the lymph-tissues and the testis having the highest degree of radio-sensitivity. The action of radium on normal tissues is described as affecting the skin, mucous membrane, cartilage and bone, blood-vessels, salivary glands, liver, pancreas, kidney, brain and spinal cord, eye, testis, ovary, and the blood. The method by which radium affects malignant tissues is based chiefly on studies of cancer of the cervix, and the various tumours are classified into three groups according to their radio-sensitivity. In this connection a strong point is made of local recurrences being much less sensitive to the action of radium than is the original growth, from which it follows that the initial dose should be the maximum compatible with safety.

The dangers of radium are fully described and illustrated under the headings of danger to the general health, local damage to tissues including necrosis of bone or cartilage, and carcinogenesis. The best method of protecting against these dangers then follows. Before entering on a detailed description of the tumours, a general discussion is given as to the value of radiation treatment. It is impossible to give an adequate summary of this important section, but it represents a fair and well-reasoned account of the pros and cons of radium, surgery, and a combination of the two methods. The clinical use of radium is increasing year by year, as is shown amongst other evidence by the tenth annual report of the British Empire Cancer Campaign, in which it is stated that the number of cases of cancer of the breast treated by radium alone had increased in three years threefold, and that the 'three-year cures' had increased sevenfold. The invention of new methods of radiation such as teleradiation and the various technical methods of applying radium have made the subject of some complexity, and it must be perfectly evident that the effective use of radium can only be undertaken by efficient teamwork accompanied by scientific research.

Part III, which represents the bulk of the book (1000 pages), consists in a consideration of the malignant tumours affecting each of the tissues and organs of the body. Each chapter deals with a particular region and gives first of all a description of the natural history of the tumour concerned, its clinical types, histology, course and termination, and diagnosis. Then follows a discussion on the choice of method of treatment, chiefly concerned with the role of radium and operative surgery. There is then a detailed account of the methods of radium application, together with a number of case histories and a consideration of the results obtained. Each part of the subject is fully illustrated, with a liberal proportion of coloured plates. Every one of these chapters is a carefully written monograph of great value. Those subjects, such as cancer of the breast, tongue, and uterus, in which radium is usually the method of first choice, are naturally treated at greatest length. In certain chapters other authors have collaborated with Mr. Cade. The chapter on intrathoracic tumours is by Price Thomas, those on the œsophagus, stomach, rectum, and anus are by Stanley Lee, and that on intracranial tumours by Denis Williams.

It is impossible to speak too highly of the thoroughness and fairness of this work. It represents the results of enormous labour, not only in clinical observation and records, but also in research and review of the literature as well as in the critical judgement required in comparing the relative values of different methods of treatment. We congratulate the author most sincerely on the successful accomplishment of his task, for which every surgeon must feel himself indebted, and also to the publishers for the very handsome way in which the book is illustrated and printed.

Field Surgery in Total War. By DOUGLAS W. JOLLY, M.B., CH.B. (N.Z.), late Major, Spanish Republican Army Medical Service. With a Foreword by Surgeon Rear-Admiral G. Gordon-Taylor, O.B.E., M.A., F.R.C.S., F.R.A.C.S. $7\frac{1}{4} \times 4\frac{7}{8}$ in. Pp. 242 + xiv, with 32 illustrations. 1940. London: Hamish Hamilton Ltd. 10s. 6d.

THE author of this clearly written practical guide to the surgery of modern warfare has had recent great experience in the practice of the subject. He was working for two years with the Spanish Republican Army and more than 4000 patients came under his care.

The book is divided into two parts, the first of which deals with the organization and tactical disposition of surgical units in the field; the second is devoted to surgical technique in forward areas. The most important matter of organization is described as the three-point forward system, which essentially consists of grouping of three units, namely, the Casualty Classification Place, the No. 1 Hospital for the most urgent cases, and the No. 2 Hospital for the lesser urgent cases. The saving of life and limb often depends on the celerity with which the patient can be submitted to treatment after he has been wounded. The object therefore of the organization is primarily directed towards reducing the 'time lag' between wounding and treatment. The general lines of surgical treatment are those with which Trueta's work has familiarized us. Sterilization of wounds is by the mechanical means of excision, and antiseptics are used very little. Anæsthesia is chiefly by ether with a simple apparatus. The sterilization of instruments is all done by dry heat, and it is pointed out how well this is adapted for having reserve sets ready for use and also how it saves the instruments in good condition. The usual warning is given about tourniquets, which are considered to have lost more lives than they saved. There is an excellent description of the arrangements for ambulances and operating theatres, so as to make the best use of heat, light, and electricity. In the treatment of injuries of the limbs, plaster-of-Paris is the main stand-by; neither the Thomas splint nor the Balkan beam is often used. Both the text and the illustrations are simple and clear, and we welcome this small text-book as being likely to be of great help in the near future.

War Wounds and Injuries. Edited by E. FLETCHER, M.A., M.B., M.R.C.P., Physician, Emergency Medical Service; Physician, Queen Mary's Hospital for the East End; etc.; and R. W. RAVEN, F.R.C.S., Surgeon, Emergency Medical Service; Surgeon to Out-Patients, French Hospital, London; etc. With a Foreword by LORD HORDER. $8\frac{1}{2} \times 5\frac{1}{2}$ in. Pp. 262 + viii, with 57 illustrations. 1940. London: Edward Arnold. 14s. net.

THIS work consists largely of articles which have appeared in the *Post-Graduate Medical Journal*, and these comprise accounts of war wounds of the various parts of the body, written by men who have had special experience. The book should prove useful to those who, happily, have not had experience of War.

Emergency Surgery. By HAMILTON BAILEY, F.R.C.S. (Eng.), Surgeon, Royal Northern Hospital, London; etc. Fourth edition. $8\frac{7}{8} \times 6\frac{3}{8}$ in. Pp. 944 + xii, with 930 illustrations, a large number in colour. 1940. Bristol: John Wright & Sons Ltd. 63s. net.

THAT four editions, in addition to two reprints, of a work on Emergency Surgery should be called for within ten years speaks well for the usefulness of this book, as well as for the endeavour of the author and publisher to keep it up to date. The original object in writing the book was to provide a guide for the isolated surgeon, and it should prove invaluable to him; nor can other surgeons engaged in emergency work afford to neglect it.

This edition is a great improvement on the last, published in 1938, both in the format and the lay-out of the subject. The publishers are to be congratulated on the number and excellence of the illustrations and also on the printing.

In comparing this with the previous edition one is impressed by the tendency to adopt more simple methods in technique, together with more thorough pre- and post-operative treatment. In the limited space of a book dealing with an unlimited subject, an author must necessarily at times be dogmatic, but if certain methods are strongly stressed, they are those which he has found useful in his own experience; and, if he has not had the opportunity of thoroughly testing some procedure then the reader is informed.

The methods and indications for infusions are given, and the importance of withholding whole blood unless the hæmoglobin content and cell-count warrant it is stressed. The simple and useful vein seeker of Ronald Edwards, which is a real advance in technique, is described and figured.

The use of sulphanilamide and similar drugs, as one expects, are mentioned in many places; perhaps their prophylactic use might be urged more. The complications—especially agranulocytosis—resulting from prolonged or large doses is not sufficiently stressed. In fact it would be an advantage if a special chapter giving in detail the dosage and therapeutic use of these drugs was added in a future edition.

The author finds it difficult to discard some of his old therapeutic stand-bys, e.g., he discards the intravenous injection of 10 per cent mercurochrome in diffuse peritonitis but recommends it almost as a routine in every other septic condition.

The chapters on the emergencies connected with the alimentary canal are very balanced and explicit; that on the appendix merits especial mention.

The chapter on gastric, duodenal, and intestinal aspiration is more than helpful and will be the means of saving many desperate cases, especially now that the sucking of a decicain lozenge (1 gr.) twenty minutes before is shown to make the passage of the tube very simple.

In this edition the treatment of Meulengracht is recommended for hæmatemesis and melæna, but the author seems to withhold the blood-drip transfusion until the condition is becoming really desperate.

He admits that ligature of the gastroduodenal artery in continuity is quite unreliable in a bleeding ulcer, so there is no point in both describing and illustrating the operation.

Thorek's method of cholecystectomy is not one to recommend in an emergency, nor is Pilbram's method of dealing with an unapproachable stone in the common bile-duct. The emergency can always be met by simple drainage of the gall-bladder or duct.

The new and timely chapters on gunshot wounds of the abdomen and war wounds in general are very welcome, though in the latter the author is unable whole-heartedly to recommend the closed plaster method, nor to discard the intravenous mercurochrome.

In this edition the author goes back to Steinmann's pin in preference to Kirschner's wire for bone extension.

The general post-operative complications are in this edition very rightly given a chapter towards the end of the book, but those especially liable to occur after abdominal and thyroid operations are given at the end of the sections dealing with these subjects, so that the reader sees them in their proper sequence and can appreciate them.

In this edition colostomy is urged as a necessary adjunct to any operation on a volvulus, but the fact that there may be a distal neoplasm causing obstruction is not mentioned.

The section on the emergencies of the female genitalia is much fuller than in previous editions, the lower-segment Cæsarian section being given to the exclusion of others.

This edition includes a very full account of thoracic emergencies, the operation for pulmonary embolectomy being beautifully illustrated.

In the previous edition no very definite lead was given on the subject of head injuries, but this has now been remedied. The author confines himself to one method only of reducing

intracranial tension, viz., mag. sulph. (1–2) per rectum, leaving any others to be carried out presumably by a surgical neurologist. It is rightly stressed that the classical text-book description of the signs and symptoms of middle meningeal hæmorrhage is the exception rather than the rule.

More space is given to emergency conditions of the vascular system. Stevenson's needle is figured and its use explained but an equally useful instrument, Key's probe is not mentioned. It is difficult to understand why indirect embolectomy is recommended for obstruction in the common iliac artery when a few pages later repair of this artery by direct suture is described and figured.

In this edition the conservative treatment of periosteomyelitis is favoured, the dictum of " treat the child and not the lesion " being followed. The author is also very nearly converted to secondary sutures of tendons and nerves. In the treatment of burns he has abandoned the rapid coagulation produced by 40 per cent tannic acid for the safe and more sure results obtained with 5 per cent.

The use of a tourniquet is favoured for emergency amputations, but no mention is made of its possible connection with the production of secondary shock. The guillotine amputation is rightly condemned in favour of the equilateral flap.

His enthusiasm for both natural and artificial maggot therapy for infected wounds may lead to more extensive trial of this method in the future.

The special emergencies of the eye, ear, nose, and throat are thoroughly dealt with by recognized authorities in these special branches.

The book can be strongly recommended and though at first sight the price appears high, it is really very cheap and very good value.

Synopsis of Operative Surgery. By H. E. MOBLEY, M.D., F.A.C.S., Chief of Surgery at St. Anthony's Hospital, Morrilton, Arkansas. $8\frac{1}{8} \times 5$ in. Pp. 375, with 339 illustrations, of which 39 are in colour. 1940. London: Henry Kimpton. 21s. net.

THIS small volume covers the whole field of operative surgery. It is unusual in that it opens with valuable chapters on the preparation for operation, anæsthesia, and post-operative care. In the second chapter it is refreshing to find that a full description is given of the drop method of administering ether, but the cumbersome Boyle's machine which fashion has for the moment made so popular in this country is not mentioned. A chapter is devoted to a full description of the methods of tying knots, but the accounts even with the diagrams are difficult to follow and cannot replace short practical exercises. In the section describing the various incisions, there are some incisions which would not be accepted by many surgeons, e.g., one along the anterior border of the sternomastoid for removal of tuberculous glands of the neck, one for removal of carcinoma of the breast which ends just below the breast, and a median incision for abdominal lesions. It is here that there appears one of the chief weaknesses of the work, that there is little or no discussion of the relative value of the methods described, or the conditions for which they should be employed. The three following chapters on the surgery of the skin, the pericardium and heart, and the arteries are all good and well illustrated, but is it necessary to divide the pectoralis minor in ligaturing the first part of the axillary artery? There is no mention of ligature of the femoral artery in Hunter's canal, and no account of the difficulties that may arise in ligature of any of the arteries. After these chapters the value of the work rapidly falls off. In the chapter on amputations, no mention is made of the old familiar names, which is a little confusing; but what is of greater importance is that no advice whatever is given as to the choice of method or as to the length of bone that should be left in order to gain a useful stump. The remaining part of the book, perhaps through haste or carelessness, contains many descriptions of operations which would be condemned by English surgeons and if advocated by students at an examination would lead to their downfall. In operations upon the Gasserian ganglion, division of the zygoma and the coronoid process of the jaw is advised. In thoracic surgery the use of the obsolete pressure chamber is advocated. In the operative treatment of an umbilical hernia a vertical ellipse is described, and no mention made of the Mayo operation; the inguinal route for the repair of femoral hernia is not described; for congenital pyloric stenosis gastro-enterostomy is advised, and Rammstedt's operation not even mentioned. Gastric ulcer without obstruction is treated by simple excision without gastro-enterostomy, and carcinoma of the stomach by the wholly useless operation of a local pylorectomy or a

sleeve resection. The later chapters are even more confused and unorthodox. In the performance of choledochoduodenostomy, complete division of the common duct with implantation of the proximal end into the duodenum is alone described, and an illustration of this operation is given with the gall-bladder still present; for carcinoma of the rectum removal of the lower colon, rectum, anal canal, and even the perianal skin all through the abdominal wound is advised and illustrated, a most hazardous and difficult procedure. Although the book is well got up and beautifully illustrated, these few examples of grave departure from the accepted teachings and practice of surgery are sufficient to indicate that it cannot be recommended as a manual for students.

Injuries of the Skull, Brain, and Spinal Cord. Neuro-Psychiatric, Surgical, and Medico-Legal Aspects. Edited by SAMUEL BROCK, M.D., New York University. 9 × 6 in. Pp. 632 + xii, with 63 illustrations. 1940. Baillière, Tindall & Cox. 38s. 6d. net.

THE physicians contributing to this volume outnumber the surgeons by about two to one, and it therefore comes about that the stress is laid more upon disturbances of cerebral function resulting from trauma than upon the surgical aspects of head injuries. To some extent it may thus be said to put surgery in its proper place, since comparatively few patients require surgical intervention after a head injury, though most will suffer from transient, and some from more persistent, disorders of cerebral activity. Furthermore, though the chapters are written by twenty-two contributors, and each could stand by itself as a brief but comprehensive account of its particular subject, there is very little overlapping. When the subjects dealt with by different authors do coincide, as, for example, cerebral concussion, which is described by a neurologist, a pathologist, and a psychiatrist, the editor has provided references from one chapter to another so that slight differences of opinion may be quickly recognized without the confusion which otherwise might result.

There is a noteworthy absence of dogmatism, the object of many of the authors being rather to state what is known about controversial matters, to provide references to the writings of others, and to leave the reader to draw his own conclusions. This method is particularly valuable in the sections dealing with the neuroses and psychotic states following head injuries, and those upon the relationship of trauma to other organic diseases of the brain and of the spinal cord, for the direct sequence of cause and effect may be difficult or impossible to prove, though the association of injury with a particular disease may be frequent enough to make this relationship a probability.

On the other hand, a more definite line of action might usefully be indicated for injuries of the spinal cord; and both the clinical aspects and the indications for operations might have been more clearly defined in the section dealing with the intracranial hæmatomas.

Surgery of the Hand. By R. M. HANDFIELD JONES, M.C., M.S., F.R.C.S., Surgeon to Out-patients, St. Mary's Hospital; Senior Surgeon, Florence Nightingale Hospital; etc. 9¾ × 6⅞ in. Pp. 140 + viii, with 95 illustrations, several in colour. 1940. Edinburgh: E. & S. Livingstone. 15s. net.

THE economic loss due to injuries and infections of the hand is so great that none can regard the present results of treatment with satisfaction. For all that has been written, these accidents, which account for over a third of the sums paid in compensation, are still widely regarded as minor surgery. Mr. Handfield Jones is concerned to set right this deplorable state of affairs, and it is not surprising to find in his book the vigorous and dogmatic style of the evangelist. The problem is twofold, first to persuade surgeons to devote to the surgery of the hand the care which its economic importance demands, and secondly to make known the best methods of treatment. This book is mainly concerned with the latter, and with the principles laid down few will quarrel. Emphasis throughout is laid on restoration of the function of the hand, and a separate chapter is given to this aspect of the subject. The first and largest section of the book deals with infection, and in the introductory chapter the author stresses the value of prophylactic measures which has been proved in many industrial concerns. For operations on the hands, the author insists on full anæsthesia either regional or general and the provision of a bloodless field. The precautions against sepsis must be as rigid as in any major operation, and the danger of secondary infection at operation or subsequent dressing is well emphasized. In separate chapters, the different anatomical types of

infection are described and details of treatment are clear and concise. For the most part the recommendations are rigid and dogmatic, perhaps more so than is necessary if the first two general principles are accepted: "Never make an incision until the presence of pus is certain", and "Never make an incision until its exact situation is known". From these it might follow that the right place to make an incision is over the pus, and although special directions are necessary for certain types, such as tendon-sheath infection, the traditional diagram with incisions shown for what the reader may take to be every contingency, stereotypes the treatment in a way that leaves no room for individual judgement. It is refreshing to see the break with tradition in the use of transverse incisions in the palm chosen for their better functional scar, but there is no reason why such incisions should not sometimes be used on the fingers also. The method of treating paronychia is open to criticism, for this infection is primarily subcuticular and the skin incisions for lifting a flap off the nail base should not be needed unless the pus is subcutaneous. In after-treatment stress is laid on movement, to be started as soon as the stage of spread is at an end. Preference is shown for light dressings, and splints are almost taboo. Chemotherapy is rightly given an important place in treatment, especially of the severe infections, but current opinion on this subject is not stable enough to warrant rules about dosage in a book which ought to enjoy more than a transient popularity; those recommended would even now be considered inadequate by some.

Easy as it is to find fault with detail in a dogmatic work, the author is to be congratulated on producing a clear guide to treatment for those inexperienced in this work. The chapter on restoration of function forms a fitting conclusion to the first section. The author's motto is to make movement the hobby of convalescence and never to allow a finger to become stiff.

The second section of the book deals with injuries of the hand along orthodox lines. The instructions for treatment of wounds are confused; in the introduction it is stated that excision is rarely necessary, but in the section on wounds of the palm excision is advised. In general, conservation of tissue is urged and amputation of digits is rightly discouraged unless it is certain that they will be useless. The treatment of divided tendons is discussed, distinction being drawn between those with and those without sheaths, but little is said about nerve injuries, which do not even appear in the index. This is the more surprising after the emphasis laid on function in early chapters, for even the division of a single digital nerve may be a grave disability in certain occupations. More might have been said, too, about foreign bodies, which at the moment are of special importance.

The third section on other surgical lesions is too brief to be of much value and gives the impression of being a make-weight. It shares with the second section a lack of balance and contains details of a random mixture of the common and the rare.

The book is profusely but not well illustrated. In the section on infections there is only one photograph of an actual case but a wealth of anatomical diagrams of doubtful value. Several pages are given to diagrams of Kanavel's spaces, the importance of which has been grossly exaggerated, and a full-page photograph of a very rare deformity is quite out of place in a work of this size.

Cancer of the Colon and Rectum: Its Diagnosis and Treatment. By FRED W. RANKIN, M.A., M.D., SC.D., F.A.C.S., Surgeon, St. Joseph's and Good Samaritan Hospitals, Lexington, Kentucky; and A. STEPHENS GRAHAM, M.D., M.S., F.A.C.S., Surgeon, Stuart Circle Hospital, Richmond, Va., and Associate Professor of Surgery, Medical College of Virginia. 10 × 6½ in. Pp. 358 + x, with 133 illustrations. 1939. London: Baillière, Tindall & Cox. 30s. net.

THE authors of this book have made a very valuable contribution to our knowledge of the symptoms, diagnosis, and surgical treatment of malignant growths of the colon and rectum, not only by recording the results of their own observations but also by correlating the opinions of several surgeons in America and abroad who take an active interest in this particular field of malignant disease.

The opening chapter of this excellent book is devoted to consideration of the anatomy and physiology of the colon and rectum. The anatomical illustrations, especially those relating to blood-supply, are very good and should be very helpful to those undertaking the surgery of this part of the intestinal tract. The distribution of the lymphatics is also well shown.

The physiology of the large intestine is fully discussed, the surgeon being reminded that it is not sufficient, when contemplating the surgery of this part of the alimentary tract,

to think in terms of anatomy alone. With this opinion we entirely agree because we are convinced that an accurate understanding of the physiology of the colon and rectum is the basis of all sound pre-operative and post-operative treatment.

The incidence, occurrence, and aetiology of cancerous growths of the colon and rectum are fully debated. The commonest site of the neoplasm is the cæcum or the sigmoid. Growths in the rectum are found at the rectosigmoid junction (69 per cent), in the ampulla (29 per cent), and in the anal canal (2 per cent).

In regard to the causation of cancer of the colon and rectum nothing definite is known, but the question as to whether an adenomatous polypus may become malignant receives considerable attention. In this connexion, the authors pay special tribute to Dukes's comprehensive review of the subject which was published in 1930.

From a pathological point of view carcinomata of the colon and rectum are classified in the following manner: (1) medullary adenocarcinoma, (2) scirrous or fibrocarcinoma, (3) mucoid (colloid) adenocarcinoma, (4) papillomatous carcinoma, (5) squamous carcinoma, and (6) melanoma.

The authors, in no uncertain manner, express their conviction that adenomata of the large intestine and of the rectum are definitely precancerous growths.

The practical application of Broders's index of malignancy and of Dukes's classification of rectal carcinomata receives ample consideration, as also does the situation of metastatic deposits in the extramural lymphatic areas.

Attention is drawn to the observation that the symptoms of a malignant growth situated in the right half of the colon differ materially from those produced by a growth in the left half. It is pointed out that signs of obstruction are usually absent or develop during the later stages of the disease when the growth is situated in the right half, but when the left half is affected obstruction makes itself manifest in the early stage and before any other symptom has had time to develop.

The diagnosis of malignant growths of the colon and rectum presents no difficulties, provided that an adequate examination is carried out in all cases that come under observation. Such an examination should consist of (1) thorough digital exploration, (2) sigmoidoscopic examination, and (3) roentgen-ray study of the colon after a barium enema has been administered.

It is claimed that differential diagnosis of growths in the colon must be made from (1) hyperplastic tuberculosis, (2) segmental chronic ulcerative colitis, (3) diverticulosis, (4) non-specific granuloma, (5) abscess of the appendix, (6) single benign tumour, (7) polyposis, (8) megacolon, (9) actinomycosis, and (10) syphilis. Each of these conditions is described at some length, as also are the details of the treatment to be adopted, but this seems to us to be somewhat superfluous in a work appertaining only to the consideration of cancer.

In the chapter dealing with operability and prognosis numerous interesting and instructive tables are included. It is pointed out that the operability-rate among surgeons varies enormously, some giving their rate as 25 per cent, whereas others operate upon over 70 per cent of their cases. It seems to us that the explanation of the discrepancy is not far to seek—i.e., the surgeon who is known to have made a a special study of cancer of the large intestine probably has a large percentage of inoperable cases sent to him for treatment, and consequently his operability-rate is low.

When dealing with the question of the choice of operation the authors strongly deprecate the modern tendency to revert to the less radical procedures which were in vogue towards the end of the last century and which were followed by a high rate of recurrence. In the case of cancer of the rectum, they also disagree with Gabriel's advocacy of a ' fluid ' one-stage operation without preliminary laparotomy. They also point out that the various two-stage combined operations now in vogue differ somewhat in technical details and in scope, but the " fundamental principle of all of them may be traced to the classical one-stage procedure of Miles ".

In making the choice of operation for a growth in the colon the type to be adopted depends upon whether the right or the left half of the colon is the seat of the disease. Thus, when the growth is situated in the right half of the colon a two-stage procedure is recommended, i.e., ileotransverse colostomy by a closed method followed by resection of the right half of the colon at a later date. When, however, the growth is situated in the left half of the

colon, the type of operation to be utilized depends upon the presence or absence of obstruction. If obstruction should have supervened, preliminary cæcostomy or a proximal transverse colostomy is recommended, and followed, at a later date, by resection of the diseased segment and end-to-end anastomosis if practicable. If, however, there are no signs of obstruction, resection and end-to-end anastomosis is all that need be done.

The details in technique of the various methods of performing resection of the colon and that of operations for excision of the rectum are all carefully described.

An excellent chapter on pre-operative and post-operative treatment follows, which will well repay close study.

We regard this book as outstanding in merit and have no hesitation whatever in recommending it to the notice of all those surgeons who are interested in, and practise the surgical treatment of, malignant disease of the colon and rectum.

Orthopædic Operations. Indications, Technique, and End Results. By ARTHUR STEINDLER, M.D., F.A.C.S., Professor of Orthopædic Surgery, The State University of Iowa, Iowa City, Iowa. $9\frac{7}{8} \times 6\frac{1}{2}$ in. Pp. 766 + x, with 322 illustrations. 1940. London: Baillière, Tindall & Cox. 50s.

THIS book will be welcomed as representing the views based on the personal experience of its distinguished author. In the preface Dr. Steindler modestly anticipates many objections and criticisms which may be made against his method of presentation. He claims that it is an honest personal experience of all the methods of operations done for orthopædic conditions, and that he does not describe anything which is outside his own practice. He divides the book into three sections: the first deals with the indication for operative treatment; the second with technique of operations; and the third with the end-results. But the result of this method of presenting his subject is that it is very difficult to get a clear idea of any particular subject as a whole. For example, the treatment of fractured neck of the femur appears in three or four different parts of the book, so that we find it very difficult to know what the author's advice is in any particular condition, and the same applies to other subjects such as congenital dislocation of the hip. In spite of its being called a book on orthopædic operations, a good deal of its space is occupied by discussions on such matters as diet and the causes of deformity. Also despite his claim that only useful and practical methods are described, the author for the sake of completeness has included many obsolete procedures, which we can hardly believe he practices at the present day, such, for example, as excision of the metatarsal heads for metatarsalgia and Foerster's operation of posterior spinal root resection. Several methods of cordotomy are mentioned, but there is no clear description, the whole subject being dismissed in seven lines. Fracture of the patella is dealt with in several different places, the use of a bone-graft is mentioned, but there is no clear description of the operative treatment advised, neither is there any mention of the removal of the fragments. The book contains a large amount of useful material, including many good illustrations and lists of references, but a number of the figures, such as those representing traction methods, are too small to be of much value.

The Head and Neck in Roentgen Diagnosis. By HENRY K. PANCOAST, M.D., Late Professor of Radiology and Director of the Department of Radiology, University of Pennsylvania; EUGENE P. PENDERGRASS, M.D., Professor of Radiology and Director of the Department of Radiology, University of Pennsylvania; and J. PARSONS SCHAEFFER, M.D., PH.D., Professor of Anatomy and Director of the David Baugh Institute of Anatomy, Jefferson Medical College, $9\frac{7}{8} \times 7$ in. Pp. 976 + xxxii, with 1251 illustrations. 1940. London: Baillière, Tindall & Cox. 69s.

THIS book is intended primarily for radiological students, but there is much in it that will be of value to surgeons specializing in diseases of the head and neck. It is beautifully illustrated, both with photographs of specimens and reproductions of radiographs, and there is a very extensive bibliography at the end of each chapter. This latter feature greatly enhances its value as a reference book for surgeons.

The first part is devoted to anatomical considerations, often of a rather elementary nature. There follow sections on fractures, bone diseases, the teeth, jaws and sinuses, mastoids, orbits, and intracranial tumours.

The sections on the lachrymal duct and cerebral pneumography (ventriculography) are of very great interest, and are finely illustrated.

The section on the localization of foreign bodies of the eye is clearly written, and should be of great help at the present time. Several methods are described, and the choice of which one to use will depend to some extent on the apparatus available. Here, as in other parts, the authors do not express their personal views very freely, but rather leave it to the student to choose for himself by experience.

BOOK NOTICES

[The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest for our readers.]

Synopsis of the Principles of Surgery. By JACOB K. BERMAN, A.B., M.D., F.R.C.S., Assistant Professor of Surgery, Indiana University School of Medicine, Indianapolis. 8 + 5 in. Pp. 615, with 274 illustrations. 1940. London: Henry Kimpton. 25s. net.

Handbook of Anæsthetics. (Formerly Ross and Fairlie). Revised by R. J. MINNITT, M.D. (Liverp.), D.A. (R.C.P. & S.Eng.), Lecturer in Anæsthesia, University of Liverpool; etc. With chapters on Local and Spinal Anæsthesia, by W. QUARRY WOOD, M.D., Ch.M., F.R.C.S.E., Surgeon, Edinburgh Royal Infirmary. Fifth edition. $7\frac{1}{8} \times 4\frac{7}{8}$ in. Pp. 364 + xiv, with 103 illustrations. 1940. Edinburgh: E. & S. Livingstone. 12s. 6d. net.

Treatment of Cancer and Allied Diseases. By 147 international authors. Edited by GEORGE T. PACK, B.Sc., M.D., F.A.C.S., Attending Surgeon, Memorial Hospital, New York; Assistant Professor of Clinical Surgery, The School of Medicine, Yale University, New Haven, and Cornell University Medical College, New York; and EDWARD M. LIVINGSTON, B.Sc., M.D., Associate Visiting Surgeon, Bellevue Hospital; Assistant Clinical Professor of Surgery, New York University College of Medicine; Assistant Attending Surgeon, Memorial Hospital, New York. In three volumes. 10 × 7 in. Vol. I, Pp. 1–920 + xc; Vol II, Pp. 921–1812 + liv; Vol. III, Pp. 1813–2598 + cxi (includes complete index). 1500 illustrations. 1940. New York and London: Paul B. Hoeber, Inc. The set, $36.00.

Surgery of Modern Warfare. Compiled by Sixty-five Contributors. Edited by HAMILTON BAILEY, F.R.C.S., Surgeon, Royal Northern Hospital, London; etc. To be issued in separate parts. $9\frac{3}{4} \times 6\frac{7}{8}$ in. Part I: Section I, Wounds: General Considerations; Section II, Wounds: Special Considerations. Pp. 1–160, with 117 illustrations, some coloured. Part II: Section II contd.; Section III, Wounds of the Trunk; Section IV, Wounds of the Blood Vessels. Pp. 161–320, Figs. 118–234. 1940. Edinburgh: E. & S. Livingstone. Each part, 12s. 6d. net.

The Art of Surgery. A Text-book for Students and Practitioners. By H. S. SOUTTAR, D.M., M.Ch. (Oxon.), F.R.C.S.(Eng.), Surgeon, London Hospital; Member of Court of Examiners, Royal College of Surgeons of England. Fourth edition. In two volumes. $7\frac{5}{8} \times 5\frac{3}{8}$ in. Pp. 779 + xvi, with numerous illustrations. 1940. London: William Heinemann (Medical Books) Ltd. 25s. net complete.

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